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Editorial

Angiocardiography: The Architectural Basis of Cardiac Function

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Angiocardiography is a technique which permits one to make observations on some aspect of the heart's form (size, shape, composition) and its contents at predetermined intervals of time. The change in form and contents at known intervals of time permits one to make observations on some aspect of the heart's function. Form and function are complementary images evoked by two different questions asked of all observable events. Form answers the question of spatial relation, and function, the accomplishment under the conditions present at the time the observations are made. Because the heart is a complex unit composed of innumerable subsidiary units, each with its own form, the individual functions of which interact with one another in an indeterminable manner to yield a resultant function, one cannot predict the form of the heart from any one of its functions. Yet, form is important not only because it is the mechanism for the generation of function but because form itself is all important in the total cost of function.

Burch¹ was the first to stress this relationship, and the importance of the size and shape of the heart was re-emphasized and its theoretical implications extended by Burton.² He reapplied Laplace's theorem to the heart. In essence, he indicated that the pressure exerted within a cardiac chamber is the product of the tension or pulling force within the muscular wall times the sum of the reciprocals of its principal radii. From this law it follows that intracardiac pressure and cardiac flow cannot by themselves determine the tension or pulling force within the musculature. For any given pressure, myocardial tension tends to increase geometrically as size increases arithmetically. It is for this reason that Burch concluded that the dilated heart is at a mechanical disadvantage, and this is perhaps why the heart's consumption of oxygen tends to be proportional to its volume and not to its external work.³

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The determination of chamber shape and volume cannot therefore be over-emphasized. Burch⁴ used Ring's electrokymographic method,⁵ developed in the Temple University Medical School's department of physiology, to estimate volume. This method is conceptually and operationally subject to large and unpredictable errors. It also idealizes volume without regard to shape, and omits the changing thickness of the muscular wall. Conceptually, the angiographic technique is ideal, and it has already been used to determine shape and estimate volume and muscular thickness.⁶⁻¹⁰

Unfortunately, there are many methodologic obstacles in the ideal application of angiography which must not be overlooked, simply because they produce systematic and reproducible errors. Obstacles related to instrumentation are rapidly being solved. Thus, for instance, the radiation hazard has been diminished by the image amplifier and by ultrashort exposure, which also eliminates blurring due to motion. There is still need for the development of a more satisfactory recording film (or paper).

As usual, the biologic obstacles are the most difficult to surmount. The contours of the cardiac chambers vary from one person to another, and in no instance fit any specific geometric shape which can be defined by a mathematical equation. Furthermore, the chambers interlock with one another so that in any single plane two or more chambers overlap. Uniplanar angiography therefore is not only useless for volumetric determination but is frequently inadequate even for localization of opacified blood. Localization is further complicated because density may vary not only with the phase of cardiac cycle but also within one chamber at the same time because of varying depth of contrast substance exposed to the roentgen ray.⁶

Localization is solved by simultaneous, and preferably stereoscopic, biplane angiography. Our group prefers the anterior and lateral projections because they are most commonly used in conventional roentgenology, positioning is easy and reproducible and its errors obvious, thereby giving more validity to linear measurements, and, finally, overlapping of chambers is minimal. With this technique the chambers' principal radii are measurable.

However, volumetric determination is not completely solved by biplane angiography. Multiplane angiography in a manner similar to Palmieri's¹¹ fluoroscopic method of reproducing the roentgenologic image of the heart as a whole is necessary for accurate determination of chamber volume. Nevertheless, the application of the biplane technique provides the best approximation of chamber volume available today.

The second biologic obstacle is the effect of the contrast substance itself. This substance is not physically identical with blood.¹² For any given substance, the smaller the volume adequate for contrast visualization and the greater the distance from the heart the injection is made, the less abnormal will be the cardiac response. This is true also for the particulate contrast substance so eloquently advocated by Dotter.¹³ This latter substance, by virtue of its discreteness of opacification, is particularly valuable for the study of flow, and has been so used¹⁴ to demonstrate continuous flow in the superior vena cava in contrast to the

phasic respiratory flow in the inferior vena cava. But again, flow must be studied at a distance from the site of the injection where it apparently represents flow of blood independent of the force of injection and the turbulence so produced.

It is for this reason that selective angiography is primarily an anatomic rather than a physiologic demonstration. This technique has been of inestimable practical value, particularly in demonstrating congenital anomalies amenable to surgical correction. However, its present practical value should not make one overlook its limitations or the importance of exploring the potentialities of the venous approach. The prime purpose of selective angiography is to define more precisely and with greater clarity a malformation previously known or suspected to be present. It is very likely that as greater confidence develops in diagnosis on clinical grounds, as experience with open-heart surgery increases, and as techniques for venous angiography improve, there will be less and less need for the selective technique. Most right-to-left shunts are recognizable by the venous technique. Teramo¹⁶ has demonstrated by the venous technique subtle abnormal flows detectable by no other method. Left-to-right shunts are also occasionally so recognizable^{16,17} by the reopacification of the right cardiac chambers. Even with a very fast circulation, so that opacification of the left heart occurs before opacification of the right heart has cleared, as is seen in infancy, negative defects make diagnosis of left-to-right shunts possible by the intravenous route.¹⁸ This technique is certainly safer than the selective route.

The angiographic technique timed by other preferably mechanical parameters, and particularly pressure, gives promise of uncovering the geometric mechanics of the heart which Burton² regards as all important. The determination of stroke volume, aortic velocity, total cardiac work, and duration of tension are all conceptually possible by this combined technique, and has already been partly so utilized by Chapman.¹⁰

The pursuit of these ideals has already led to many unanticipated by-products of inestimable practical and theoretical value. One can point to the numerous circulatory abnormalities uncovered by angiography in contrast to the paucity of such reports in the pre-existing clinical or even pathologic literature. A review of angiographic discoveries is beyond the scope of this editorial, but a few examples may emphasize the inadequacy of interpretation based purely on functional findings.

Angiography has demonstrated that pericardial involvement is frequent in many systemic diseases. Pericardial effusion at times forms a significant fraction of the cardiac silhouette in congestive failure.¹⁹ Pressure and flow alone can neither predict the presence nor evaluate the significance of this factor.

Increased pulsations of the left lower pole of the heart in left ventricular enlargement due to hypertension or other causes is difficult to explain on the basis of a normal or subnormal cardiac output. In such instances, angiography has clearly demonstrated enlargement of the left atrium comparable to that seen in mitral valvular disease. Mitral regurgitation masking part of the cardiac output could explain these findings; and this possibility should be explored. It has already been demonstrated that esophageal displacement is

a poor criterion of left atrial volume, particularly so when cardiac enlargement is present.²⁰ Tricuspid regurgitation is suggested by enlargement of the superior vena cava not otherwise explained.

For technical reasons, our group studies pressure flow and volume in immediate succession rather than simultaneously. Pressure and flow are measured under basal conditions. Volume and flow (as determined by opacification of blood) are measured under conditions imposed by venous angiography. Fortunately, this state makes little difference so far as volume is concerned. Little, if any, abnormal course of flow is produced by this technique. The velocity of flow, however, is certainly different from that present in the basal state. Such flow studies are also not quantitative (although density is used as a rough index of quantity). The error, however, is systematic and reproducible, as indicated by identical findings from year to year on patients with static cardiac disability. Such studies are valuable in uncovering hidden fallacies in the interpretation of cardiac output by demonstrating abnormal course of blood not otherwise detectable.

By an analysis of these three factors it becomes clear that the concept that rheumatic heart disease with mitral stenosis is simply stenosis of the mitral valve is as gross an exaggeration as the preceding prevailing concept that stenosis of the mitral valve is of little significance in rheumatic heart disease with mitral stenosis. A similar type of analysis is applicable to other complex cardiac lesions. In addition, the relation of muscular thickness to diastolic capacity is of particular importance in the evaluation of left ventricular performance.

These remarks are intended to emphasize the fact that without a knowledge of the heart's architecture, one cannot know what the heart has to do to perform any specific task.

REFERENCES

1. Burch, G. E., Ray, C. T., and Cronvich, J. A.: Circulation **5**:504, 1952.
2. Burton, A. C.: Am. HEART J. **54**:801, 1957.
3. Visscher, M. B.: Minnesota Med. **21**:85, 1938.
4. Burch, G. E., Cronvich, J. A., Creech, O., and Hyman, A.: Am. HEART J. **53**:890, 1957.
5. Ring, G. C., Balaban, M., and Oppenheimer, M. J.: Am. J. Physiol. **157**:343, 1949.
6. Soloff, L. A., Zatuchni, J., Stauffer, H., and Kelly, E.: Circulation **13**:334, 1956.
7. Soloff, L. A., Zatuchni, J., and Mark, G. E., Jr.: Circulation **15**:430, 1957.
8. Arvidsson, H.: Acta radiol., Suppl. **158**, 1958.
9. Soloff, L. A., and Zatuchni, J.: Am. J. M. Sc. **234**:313, 1957.
10. Chapman, C. B., Baker, O., Reynolds, J., and Bonte, F. S.: Circulation **18**:1105, 1958.
11. Palmieri, G. C.: Gior. clin. med. **1**:146, 1920.
12. Gidlund, Å.: Acta radiol., Suppl. **130**, 1956.
13. Dotter, P. T., and Frische, L. H.: Circulation **18**:961, 1958.
14. Stauffer, H. M., and Carter, B.: Unpublished observations.
15. Teramo, M.: Sc. med. ital. **5**:No. 1, 1956.
16. Soloff, L. A., and Zatuchni, J.: Am. J. M. Sc. **232**:528, 1956.
17. Soloff, L. A., and Zatuchni, J.: Am. J. M. Sc. **233**:167, 1957.
18. Astley, R.: Proc. Roy. Soc. Med. **50**:1024, 1957.
19. Soloff, L. A., Zatuchni, J., Stauffer, H. M., Carter, B., and Winters, W., Jr.: Unpublished observations.
20. Soloff, L. A., and Zatuchni, J.: Am. J. Med. **21**:551, 1956.
21. Soloff, L. A., Zatuchni, J., and Mark, G. E., Jr.: Am. J. M. Sc. **233**:518, 1957.

Clinical Communications

The Use of Amyl Nitrite in the Differentiation of Fallot's Tetralogy and Pulmonary Stenosis With Intact Ventricular Septum

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In previous communications concerning the differentiation of Fallot's tetralogy from severe pulmonary stenosis with intact ventricular septum and right-to-left interatrial shunt, attention was drawn to the striking difference in the duration of the systolic murmur.^{1,2} In the tetralogy the murmur usually reaches a crescendo near mid-systole and ends either before or at the loud aortic second sound, which it does not obscure. In severe pulmonary stenosis with intact ventricular septum the murmur is much more prolonged, reaching a crescendo late in systole and extending well beyond the aortic second sound, which it often completely obscures. The murmur ends before a very soft pulmonary second sound which is very widely separated from the aortic component. This difference in behavior of the murmurs can be appreciated at the bedside and the diagnosis usually settled by auscultation.

In a subsequent publication³ it was shown that the length of the systolic murmur closely reflects the severity of the stenosis. However, the murmur behaves in opposite fashion in the two conditions with increasingly severe stenosis. Thus, in pulmonary stenosis with intact ventricular septum the more severe the stenosis the longer and later the murmur. In Fallot's tetralogy the more severe the stenosis the shorter and earlier the murmur. A successful valvotomy or infundibular resection has an opposite effect on the murmur, shortening

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it in the former and lengthening it in the latter condition, so that accurate prediction of the operative result can be made from auscultation. These striking differences were shown to be due to the different dynamic situation in the two conditions.

Occasionally, however, it is difficult to distinguish between mild Fallot's tetralogy (cases often acyanotic at rest) and moderately severe pulmonary or infundibular stenosis with intact ventricular septum. In both conditions long systolic murmurs are found extending into the aortic second sound but not obscuring it. In both, wide splitting of the second sound with a delayed soft pulmonary component occurs.³ Moreover, the similar clinical, electrocardiographic, and radiologic features, as well as the similar right ventricular and systemic systolic pressures found during cardiac catheterization, add to the diagnostic difficulties. Accurate diagnosis is essential in planning the surgical procedure.

The purpose of this paper is to show that inhalation of amyl nitrite induces an opposite effect on the length and loudness of the systolic murmur in the two conditions, and that this is dependent on the striking difference induced on the right ventricular pressure by this drug.⁴ This harmless procedure may be used either at the bedside or during cardiac catheterization, and is of great value in establishing the diagnosis, particularly when the auscultatory and manometric findings of the two conditions overlap. Furthermore, it is of value in differentiating other acyanotic congenital cardiac conditions associated with a pansystolic parasternal murmur which occasionally closely simulate pulmonary or infundibular stenosis with intact ventricular septum.¹⁴ Its use in differentiating aortic ejection from mitral regurgitant systolic murmurs has been shown by Barlow and Shillingford.¹⁵

MATERIAL AND METHODS

There were 22 cases of Fallot's tetralogy, 12 cases of pulmonary stenosis with intact ventricular septum, and 3 cases of infundibular stenosis with intact ventricular septum. The diagnosis was proved in all cases by cardiac catheterization, selective angiography from the right ventricle, surgery, or necropsy, on the basis of criteria previously described.^{1,2} Furthermore, the cases studied represented varying degrees of severity in each condition. No case was accepted if any doubt remained as to whether or not the ventricular septum was intact.

The effects of amyl nitrite on the systemic and right ventricular pressures were studied during cardiac catheterization in 10 cases of tetralogy, 8 cases of pulmonary stenosis with intact ventricular septum, and 2 cases of infundibular stenosis with intact ventricular septum. At the end of a routine diagnostic cardiac catheterization a control recording was made of the right ventricular and systemic pressures (brachial or femoral artery), together with a high-frequency phonocardiographic (PCG) tracing using the N.E.P. multichannel recording apparatus. Immediately consecutive right ventricular and systemic pressures were recorded through a two-way tap attached to the manometer head.¹⁷ The PCG was recorded at the same attenuations throughout, and frequent recordings at fast paper speed (75 mm. per second) were made during held expiration throughout the study. Between the fast strips the recordings were made at slow paper speed (2.5 or 8 mm. per second). The patient was encouraged to take deep inhalations of amyl nitrite for approximately 15 seconds. The changes in the systemic and right ventricular pressures were monitored on an oscilloscope and recorded continuously at slow speed, interspersed with frequent short recordings at fast speed. Samples of blood were taken from the right ventricle and systemic artery before inhalation of amyl nitrite, and on several occasions during the peak action of the drug. This was of secondary importance in this study, inasmuch as the main purpose was to obtain pressure recordings and PCG tracings during the brief period of action by amyl nitrite.

After the pressures and pulse rate had returned to a constant level (usually by 4 minutes), the inhalation of amyl nitrite was repeated, the main object being to produce a significant drop in the systemic pressure. If the patient cooperated well, the tests were soon over, but in small infants and uncooperative patients several attempts were often required. If the patient strained, a Valsalva effect was produced, causing misleading results. During general anesthesia the effect of amyl nitrite is less marked, presumably because of vasodilatation induced by the anesthetic.

A parallel study was also made on outpatients attending the Cardiac Clinic, who were deliberately selected to show the effect of amyl nitrite on cases of different severity.³ A control PCG tracing was recorded with one microphone at the site of maximum intensity of the murmur and one at a suitable site (usually at the fourth left intercostal space) to record the aortic second sound, together with an ECG lead. Ten deep inhalations of amyl nitrite usually produced the desired brisk fall in blood pressure, flush, and tachycardia. Phonocardiograms were recorded continuously during and after the inhalation, and frequent fast tracings (75 mm. per second) were made during held expiration throughout the study. Recordings with constant amplification were made during held expiration in order to assess accurately any change in the intensity of the murmur and heart sounds.

The duration of the inhalation was noted and a signal registered at intervals of 7.5 seconds after withdrawal of the ampule. Blood pressure readings (cuff method) were taken at very frequent intervals by one of us, while the other observed the changes in the murmur through the audiophone. Recordings were continued until the murmur had returned to its initial intensity and length, which usually required 3 to 4 minutes. The study was usually repeated at least once.

RESULTS

Fallot's Tetralogy.—

Effect on the systemic and right ventricular pressures: The effect of inhaled amyl nitrite on systemic and right ventricular pressures was studied in 10 cases of the tetralogy and is shown in Table I. In each case, during the first 15 to 30 seconds, there was a fall in both the systemic and right ventricular systolic pressures (Fig. 1). The fall in the systemic systolic pressure (average, 19 mm. Hg) was always slightly greater than the fall in right ventricular systolic pressure (average, 15 mm. Hg). In no case did the right ventricular systolic pressure rise during nor immediately after the maximal effect of the drug, provided the subject was not straining or crying. There were usually marked tachycardia and increased cyanosis immediately after inhalation. As the effect of the drug wore off, the systemic and right ventricular pressures gradually rose, while the tachycardia and cyanosis diminished, and the resting state was usually reached within 4 minutes.

During the inhalation, ear oximetry showed a sharp fall in the systemic arterial oxygen saturation, indicating an increase in right-to-left shunt (Fig. 1). As the effect wore off, so the arterial oxygen saturation gradually rose to the initial level. Ear oximetry was most useful in detecting slight transient cyanosis in mild cases in which there was acyanosis at rest.

Effect on the systolic murmur and heart sounds: During the first 30 seconds after the inhalation of amyl nitrite the pulmonary systolic murmur diminished in length and intensity in every case. This could be readily appreciated by the ear despite the marked tachycardia during the maximal effect of amyl nitrite. Thereafter, as the effect wore off, the systolic murmur increased in length and intensity and returned to its original state in about 3 minutes. The clinical observations were confirmed in each case by the PCG tracing, which also showed

TABLE I. THE EFFECT OF INHALATION OF AMYL NITRITE IN FALLOT'S TETRALOGY AND PULMONARY STENOSIS

NUM-BER	CASE AGE, SEX	SEVER-ITY (1-4)	BEFORE AMYL NITRITE				MAXIMAL EFFECT OF AMYL NITRITE				AFTER AMYL NITRITE			
			SYSTEMIC B.P. (MM. Hg)	RVP (MM. Hg)	ART. O ₂ (%)	R.V. O ₂ (%)	SYSTEMIC B.P. (MM. Hg)	RVP (MM. Hg)	ART. O ₂ (%)	R.V. O ₂ (%)	SYSTEMIC B.P. (MM. Hg)	RVP (MM. Hg)	ART. O ₂ (%)	R.V. O ₂ (%)
<i>Fallot's Tetralogy</i>														
1.	T.S. 18, M	1	120/80	117/5	93	57	95	100/69	100/0	—	—	110	125/82	117/0
2.	F.S. 24, F	2	95/65	105/5	61	40	80	80/58	90/5	—	—	83	105/68	112/5
3.	W.J. 4, M	2	90/50	100/5	—	—	163	82/45	82/2	—	—	155	—	110/5
4.	B.O. 6, M	2	35/70	95/0	65	57	95	60/42	82/-5	—	—	140	85/60	103/0
5.	A.P. 22, F	2	105/75	112/0	73	—	120	90/70	105/0	66	—	128	105/67	107/0
6.	M.J. 4, F	2	110/ 105/0	75	55	98	90/ 93/5	—	—	—	145	110/ 102/0	—	—
7.	M.B. 8, M	3	95/60	103/0	48	36	130	75/50	75/0	—	—	150	86/50	100/0
8.	T.K. 6, M	3	82/50	95/0	13.9	—	125	67/38	80/0	13.3	—	135	82/52	100/0
9.	C.K. 3, F	3	—	57/-1	26	11	145	—	43/-1	—	—	150	—	70/1
10.	P.K. 3, M	4	75/50	75/0	—	—	90	—	63/0	—	—	100	—	70/5

DIAGNOSTIC VALUE OF AMYL NITRITE TEST

Pulmonary Stenosis

	P.V. 16, F	1	135/80	25/3	92	72	98	100/50	53/3	—	—	125	140/90	30/3	93	72	105
1.	H.B.	1	137/100	60/2	96	66	95	80/56	100/2	—	—	110	115/70	55/2	95	73	76
2.	T.S. 8, M	1	95/60	52/5	86	66	84	72/35	100/-5	87	—	140	108/65	62/6	86	—	92
3.	B.V. 13, F	2	120/85	72/0	86	67	120	60/40	115/0	—	—	160	125/80	90/0	—	—	—
4.	D.D. 7, M	2	75/48	80/-5	90	65	140	45/20	135/-5	—	—	150	—	—	85/0	—	—
5.	A.S.* 6, F	2	120/75	92/10	94	64	105	70/42	155/15	—	—	160	135/95	100/20	89	60	130
6.	J.S.* 16, M	3	130/60	108/0	92	71	80	75/35	136/0	96	72	96	125/62	130/0	95	72	85
7.	K.T. 30, M	3	200/120	142/3	95	70	66	100/75	>20/3	—	—	105	195/120	160/5	—	—	74
8.	J.P. 16, F	3	120/72	124/8	91	62	118	63/42	185/10	91	71	160	142/92	160/0	91	—	135
9.	T.S. 8, M	3	120/65	125/10	80	55	78	90/48	182/5	82	58	98	113/65	136/8	77	58	85
10.																	

*Infundibular stenosis.

that the first sound became loud, because of tachycardia, and the aortic second sound soft, because of the fall in systemic diastolic pressure.⁵ A similar effect was noticed in all cases of tetralogy, whether extreme (1 case), severe (4 cases), moderate (5 cases), or mild (12 cases) (Figs. 4 and 5). The method of grading severity was based on criteria described elsewhere.³ In the extreme case the murmur disappeared completely during the peak action of amyl nitrite, and a similar effect was recorded in 2 of the 4 severe cases studied. In one of these cases the initial short early systolic murmur buried an aortic ejection sound.

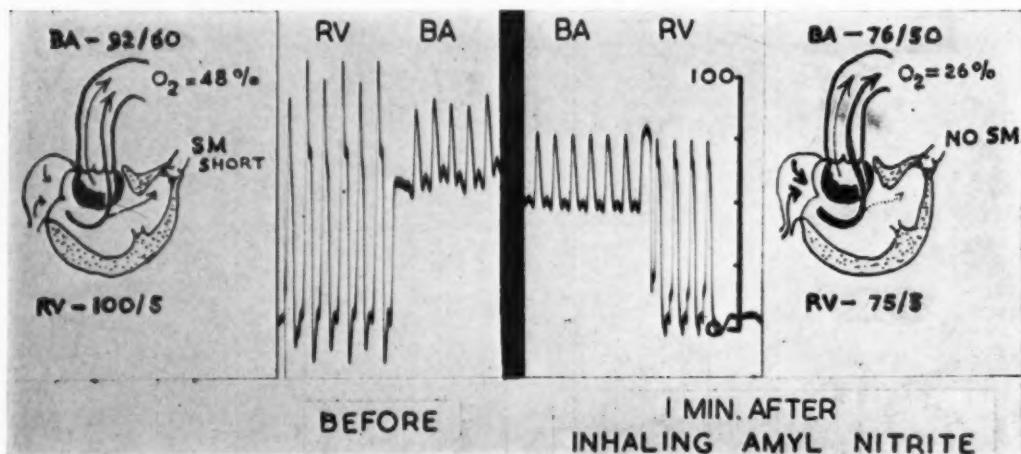


Fig. 1.—Severe tetralogy. Effect of amyl nitrite on immediately consecutive right ventricular (RV) and brachial artery (BA) pressures and arterial oxygen saturation. One minute after inhalation the BA and RV pressures dropped from 92/60 and 100/5 to 76/50 and 75/5 mm. Hg., respectively, and arterial oxygen saturation dropped from 48 to 26 per cent. The pulmonary systolic murmur temporarily disappeared, reflecting marked reduction in pulmonary blood flow.

However, when the murmur became much softer and earlier during the effect of amyl nitrite, the aortic ejection sound was clearly shown (Fig. 4). In the 5 moderately severe cases there was marked softening and shortening of the duration of the murmur during the peak action of the vapor. In one case sinus bradycardia persisted throughout, showing that in the tetralogy the shortening of the murmur is due to factors other than the sinus tachycardia induced by amyl nitrite.

In all 12 mild cases the systolic murmur was loud and long, extending into the aortic second sound but never completely obscuring it (Fig. 5). In 9 of these cases a soft pulmonary component could be recorded, causing wide splitting of the second sound (average, 0.08 second). The graphic appearance of the murmur in relation to the aortic second sound and the width of splitting was indistinguishable from that of moderately severe pulmonary stenosis with intact ventricular septum, wherein the right ventricular systolic pressure is between 60 and 120 mm. Hg.³ The murmur was never as prolonged, even in the mildest tetralogy, as in severe pulmonary stenosis with intact ventricular septum.³ In all these mild cases (including one case that had been converted from an extreme tetralogy into a mild acyanotic tetralogy by a successful valvotomy) the murmur became

much reduced in intensity, and shortened considerably. No case was encountered with a completely negative result, although the shortening of the systolic murmur was much more marked in some mild cases than in others. This must be related to the degree of cooperation of the patient, the lability of the vascular responses, and, possibly, the size of the ventricular septal defect.

In all 9 cases of mild tetralogy with a recordable pulmonary sound this sound disappeared during the maximal effect of amyl nitrite, and returned thereafter (Fig. 5). In one of these cases an incompetent pulmonary murmur followed the delayed sound and both disappeared during the maximal effect of amyl nitrite. These observations support the conjecture that pulmonary blood flow diminishes and pulmonary arterial pressure drops in association with the known drop in right ventricular systolic pressure. In fact, a drop in pulmonary arterial pressure during inhalation of amyl nitrite in cases of the tetralogy has been reported by Wood.⁶

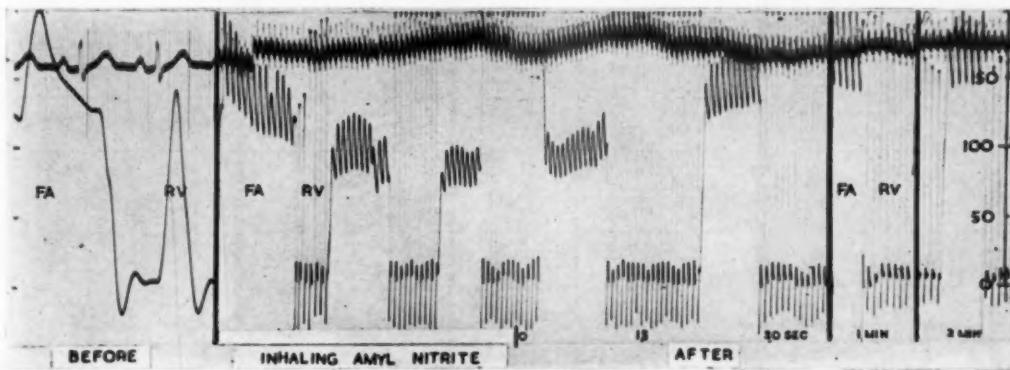


Fig. 2.—Severe pulmonary stenosis with intact ventricular septum. Effect of amyl nitrite on immediately consecutive femoral arterial (FA) and right ventricular (RV) pressures. Before amyl nitrite the FA and RV pressures were 200/120 and 142/0 mm. Hg, respectively. Cardiac rate was 68/min. During the 30 seconds of inhalation, FA pressure fell rapidly to 100/72 mm. Hg, while RV pressure rose steeply with each successive systole to reach a level exceeding 200 mm. Hg, the cardiac rate increasing to 100/min. After cessation of inhalation, FA pressure rose, reaching 175/135 after 30 seconds, 200/145 after 1 minute, and 195/146 mm. Hg after 2 minutes, while cardiac rate slowed to 78/min. RV pressure, however, remained much elevated throughout the 2 minutes, and although commencing to fall after 1 minute, it was still high (160/5 mm. Hg) at 2 minutes.

In a few cases, loud third and atrial sounds emerged for a short while and then quickly disappeared, even though the murmur remained short. The appearance of these sounds suggested rapid flow of blood into and through the right ventricle during the early phases of action of the drug.

Pulmonary and Infundibular Stenosis With Intact Ventricular Septum.—

Effect on the systemic and right ventricular pressures: The effect of inhaled amyl nitrite on the systemic and right ventricular pressures was studied in 8 cases of pulmonary valvular stenosis and 2 cases of infundibular stenosis, the cases being selected to cover a wide range of severity. There were 3 mild cases (right ventricular systolic pressure [RVP] under 60 mm. Hg), 3 moderately severe cases (RVP, 60 to 120 mm. Hg), one of whom had infundibular stenosis, and 4 severe cases (RVP, 120 to 180 mm. Hg), one of whom had infundibular

stenosis. The results are shown in Table I and indicate that whether the stenosis (valvular or infundibular) was mild, moderate, or severe the effect of amyl nitrite on the pressures was the same. In each case, during the first 15 seconds of inhalation of amyl nitrite, there was a quick fall in the systemic pressure and pulse pressure associated with a marked tachycardia. Within 10 seconds the pressure in the right ventricle began to rise rapidly with each successive beat (Fig. 2). After 20 or 30 seconds the systemic pressure was usually very low and the right ventricular pressure very high (Figs. 2 and 3). When the inhalation of amyl nitrite was stopped, the systemic pressure returned gradually to the basal level, but the right ventricular systolic pressure continued to rise and took much longer to return to normal than the systemic pressure (Fig. 3).

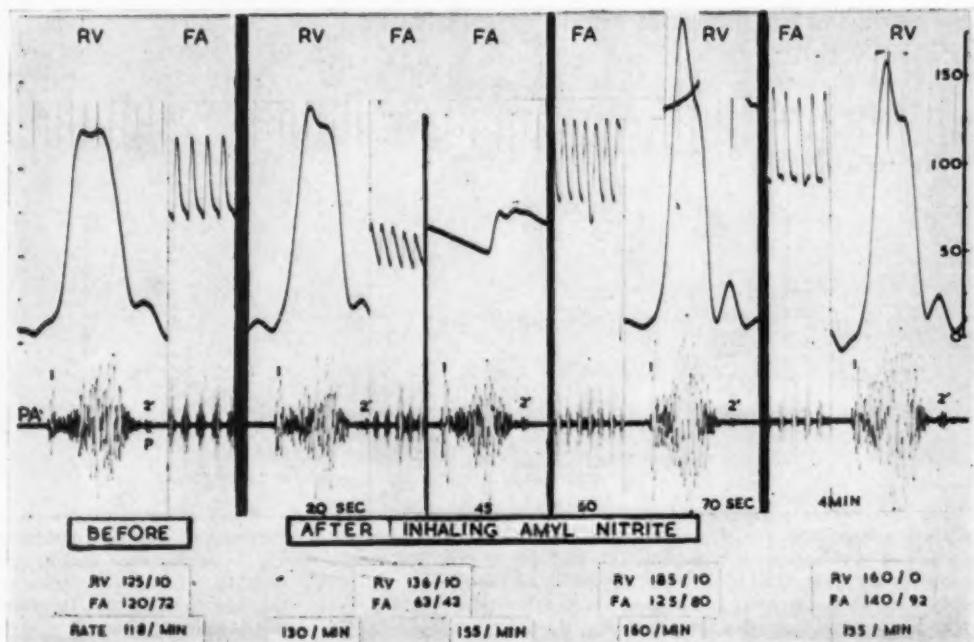


Fig. 3.—Severe pulmonary stenosis with intact ventricular septum. Before amyl nitrite the immediately consecutive RV and FA systolic pressures were almost equal, simulating Fallot's tetralogy. The systolic murmur at the pulmonary area (PA) was very prolonged, obscuring the aortic component, but ending before the very much delayed soft pulmonary component (2.P.). After inhalation, the marked drop in systemic pressure followed by marked rise in RV pressure proved that the ventricular septum was intact. Note the much quicker return to normal of FA than RV pressure. The FA pressure reached resting level in 1 minute, after which there was an overshoot. The highest RV pressure was reached at 70 seconds, and even at 4 minutes it still exceeded the resting level. The systolic murmur increased in intensity with the rise in RV pressure, being loudest at 70 seconds and still increased at 4 minutes. The pulmonary component persisted throughout. Oxygen saturation of the RV blood rose from 62 to 71 per cent during the peak effect, while systemic oxygen saturation remained unchanged at 91 per cent.

Thus, the peak rise in right ventricular pressure usually occurred well after the peak fall in systemic pressure. In several cases the systemic pressure subsequently rose well above the basal level, with an increased pulse pressure, suggesting an overshoot phenomenon (Fig. 3). By 4 minutes the right ventricular pressure usually had returned to the initial level. The average fall in systemic

systolic pressure was 50 mm. Hg, while the average rise in the right ventricular pressure was 58 mm. Hg. These changes in pressure were therefore much more dramatic than those seen in the tetralogy. However, the most important diagnostic feature was the marked rise in right ventricular pressure, as opposed to its fall in the tetralogy. The divergent behavior of the pressures following inhalation of amyl nitrite readily distinguished those cases of pulmonary stenosis with intact ventricular septum in which equal systemic and right ventricular systolic pressures simulated the tetralogy (Fig. 3). Conversely, the response to amyl nitrite should also identify cases of tetralogy with discrepant right ventricular and systemic systolic pressures simulating stenosis with intact ventricular septum.^{2,7-9}

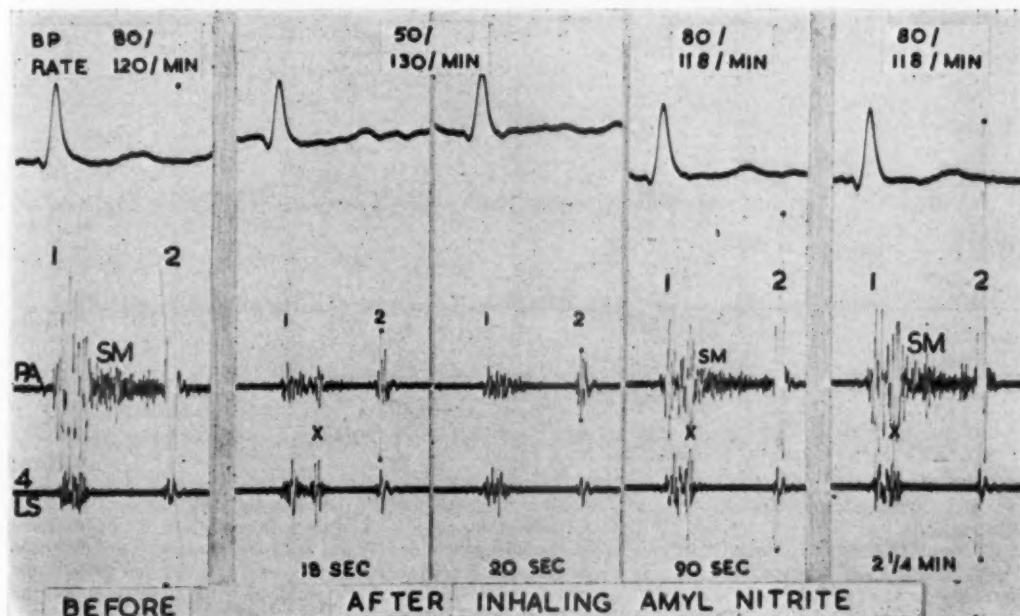


Fig. 4.—Severe tetralogy. Before amyl nitrite there was a soft systolic murmur which had an early crescendo and ended just before the very loud aortic second sound (2). Eighteen seconds after inhalation the murmur disappeared, exposing an aortic ejection sound (X). Two seconds later the ejection sound either disappeared or became much closer to the first heart sound. Gross diminution in intensity of the aortic second sound reflected the marked fall in systemic diastolic pressure. After 90 seconds, with the rise in blood pressure (and presumably in RV pressure), both murmur and ejection sound reappeared, and by 2 1/4 minutes the murmur had returned to the resting state. Each vertical line measures 0.04 sec. in this and subsequent phonocardiograms.

In cases without a right-to-left interatrial shunt there was no fall in systemic oxygen saturation, but this might be anticipated in cases with an atrial septal defect. Data on the change in oxygen saturation in the right ventricle were not adequate, and, in the main, were disappointing. A rise in oxygen saturation of the blood returning to the right heart would be anticipated following the sudden release of peripheral resistance. Those samples of blood taken during the peak action of amyl nitrite all showed a slight rise in oxygen saturation (Table I and Fig. 3). However, the technique used was too crude to detect

small evanescent changes in oxygen saturation. Moreover, this study was designed mainly to determine changes in pressure, which meant that sufficient samples could not be taken for oxygen estimation at the height of the circulatory changes. A catheter with double lumen was used on only one occasion, and by this means pressure and oxygen saturation data could be obtained simultaneously. This aspect is being investigated further.

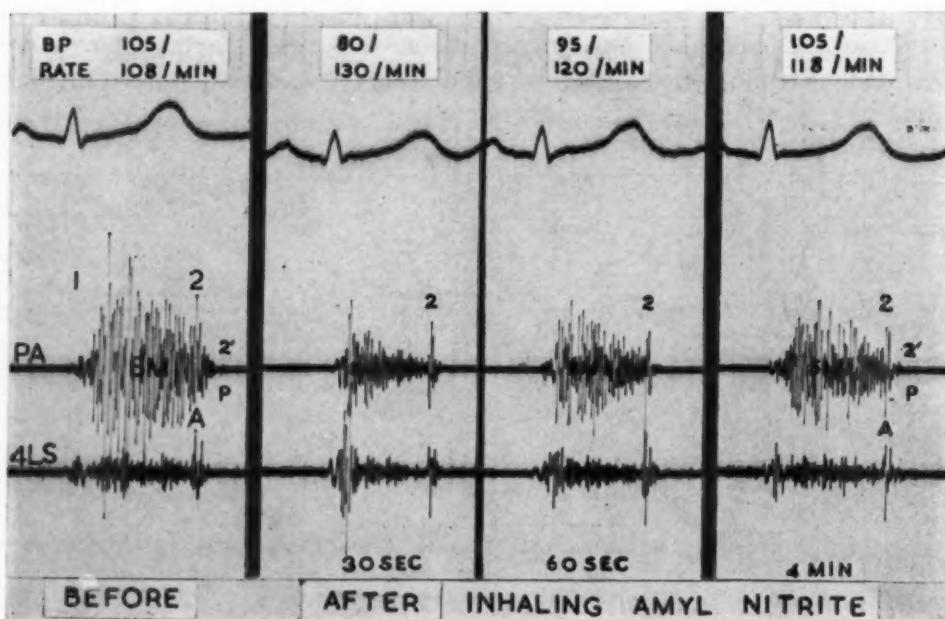


Fig. 5.—Mild (acyanotic) tetralogy. Before amyl nitrite the loud prolonged systolic murmur filled systole but did not obscure the aortic component (2,A). A very soft and delayed pulmonary component (2,P) was recorded 0.07 sec. after the aortic sound. These findings were indistinguishable from those of moderately severe pulmonary or infundibular stenosis. However, the marked temporary reduction in the intensity of the murmur with the disappearance of the pulmonary component following amyl nitrite proved Fallot's tetralogy. Compare with Fig. 6.

Effect on the systolic murmur and heart sounds: The effect of inhaled amyl nitrite on the auscultatory and PCG findings was studied in 5 mild cases, 6 moderately severe cases, 2 of whom had infundibular stenosis, and 4 severe cases, one of whom had infundibular stenosis. The changes induced during and after the inhalation were similar in all cases studied and quite different from those found in Fallot's tetralogy (compare Figs. 3 and 6 with Figs. 4 and 5). During the inhalation, while the systemic pressure was falling, the systolic murmur became much louder. This indicates that the reduced systemic pressure is accompanied by an increase in pulmonary flow unlike the response found in the tetralogy. During the period after inhalation, while the pulse rate was slowing, the murmur became even louder and more prolonged, reflecting the continued rise in right ventricular pressure, but usually after 4 minutes it had returned to its original intensity and duration.

The increase in loudness was invariably confirmed by the PCG tracing,

and the crescendo often appeared a little later in systole, suggesting prolongation of right ventricular systole in relation to left ventricular systole. Left ventricular systole might shorten while right ventricular systole lengthens during the peak action of the drug. This should result in a systolic murmur of increased duration in relation to the aortic second sound and a greater width of splitting.³ However, it was difficult to compare the width of splitting before and during inhalation of amyl nitrite because of the marked difference in heart rate. The fact that the width of splitting, when measurable, remained virtually unchanged during the severe tachycardia must mean that there was either prolongation of right ventricular systole or shortening of left ventricular systole, or both (Figs. 3 and 6).

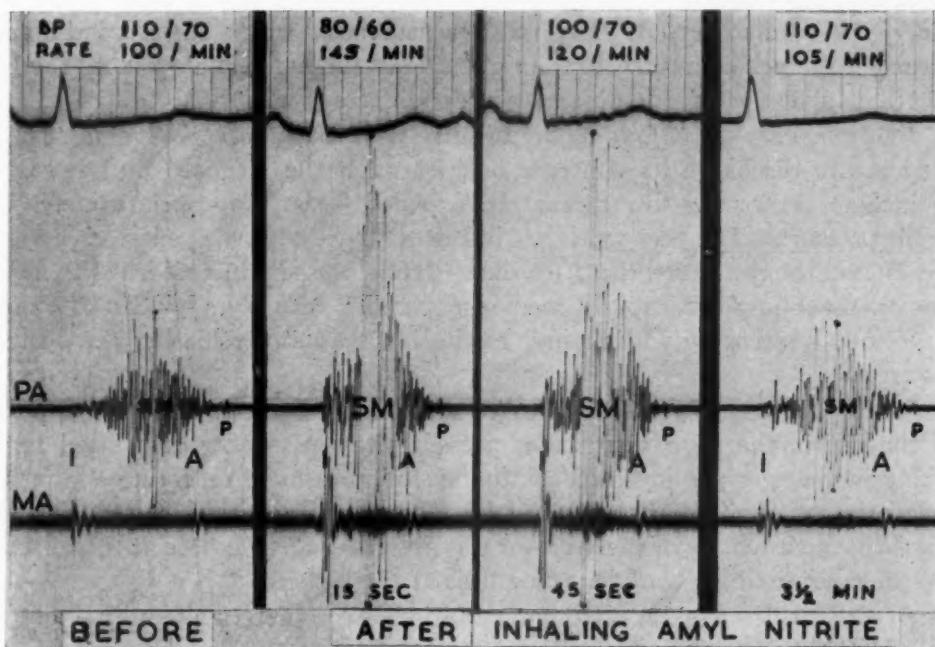


Fig. 6.—Moderately severe pulmonary stenosis with intact ventricular septum. The crescendo and duration of the murmur and wide splitting of the second sound could not be distinguished from those in mild acyanotic Fallot's tetralogy. However, the gross increase in loudness of the murmur with persistence of the pulmonary component (*P*) after amyl nitrite proved that the ventricular septum was intact.

The pulmonary component never disappeared, as occurred in all cases of mild tetralogy showing a recordable pulmonary component (compare Figs. 3 and 6 with Fig. 5). This suggests that the pulmonary blood flow and pressure were well maintained and probably moderately increased by the high right ventricular pressure. The fact that the pulmonary component never greatly increased in loudness may indicate that the pulmonary arterial pressure never rose much, despite the marked rise in right ventricular pressure. The effect of amyl nitrite on the pulmonary arterial pressure was measured in only one case. The pressure rose from 15/5 to 23/10 mm. Hg, remaining at this level for a minute after cessation of the inhalation. The RVP rose from 72/0 to 115/0 mm. Hg during a separate inhalation. The pulmonary component remained unchanged through-

out the synchronously recorded PCG tracing, while the murmur became greatly increased in intensity as well as prolonged in relation to the aortic second sound.

An atrial sound emerged in the occasional case during the inhalation but quickly disappeared as the cardiac rate slowed down.

COMMENT

The strikingly different response of the right ventricular pressure to overfilling with blood following the inhalation of amyl nitrite forms the basis of the different behavior of the systolic murmur in the two conditions. Amyl nitrite presumably acts by suddenly releasing the systemic peripheral resistance, resulting in a pronounced fall in systemic pressure and a marked tachycardia with an increased cardiac output. This must be associated with a sudden and marked increase in the venous return to the right side of the heart analogous to the tidal wave that follows the sudden opening of flood gates (Fig. 7).

In pulmonary or infundibular stenosis with intact ventricular septum the ventricle can discharge its contents only through the stenosed outlet, so that any increase in venous filling must be expelled by an appropriate increase in systolic pressure. The very steep rise in this pressure with each successive systole (Fig. 2), and the continued rise after the systemic pressure has returned to normal (Fig. 3), must imply a rapidly increasing venous return and indirectly reflect the profound extent to which amyl nitrite is capable of releasing the systemic resistance.

Similar changes in pressure occurred whether the stenosis was mild or severe, and the rise in the right ventricular pressure was invariably associated with a striking increase in the intensity of the systolic murmur, reflecting the marked increase in the speed and volume of blood ejected through the stenosis. The increase in the intensity of the murmur was always easy to appreciate on auscultation, thus permitting a confident diagnosis at the bedside.

In Fallot's tetralogy the dynamic situation is completely altered by the presence of a large ventricular septal defect, which offers to the right ventricle an escape route of much less resistance than its stenosed outflow tract, and hence the right ventricular pressure cannot significantly exceed the systemic pressure. Thus, the right ventricular pressure is determined not by the severity of the stenosis, as in the case of stenosis with an intact ventricular septum, but by the systemic resistance.* Pulmonary blood flow is therefore dependent on two main factors, namely, the systemic resistance and the severity of the stenosis. For a constant systemic resistance, pulmonary blood flow is inversely proportional to the severity of the stenosis, as shown by the inverse relation between the length and loudness of the murmur and the severity of the stenosis, in contrast to the direct relation found in cases with an intact ventricular septum.^{1,3} Conversely,

*This argument holds for the majority of cases of tetralogy in which the ventricular septal defect is large. It is appreciated that in the rare case of an exceptionally small septal defect,^{3,7} or a large defect rendered functionally small by a tricuspid or endocardial flap valve,^{10,18} the severity of the stenosis becomes the determining factor in the level of the right ventricular pressure. In fact, the smaller the defect the more closely will the behavior of the right ventricular pressure and murmur before and after amyl nitrite simulate stenosis with an intact ventricular septum.

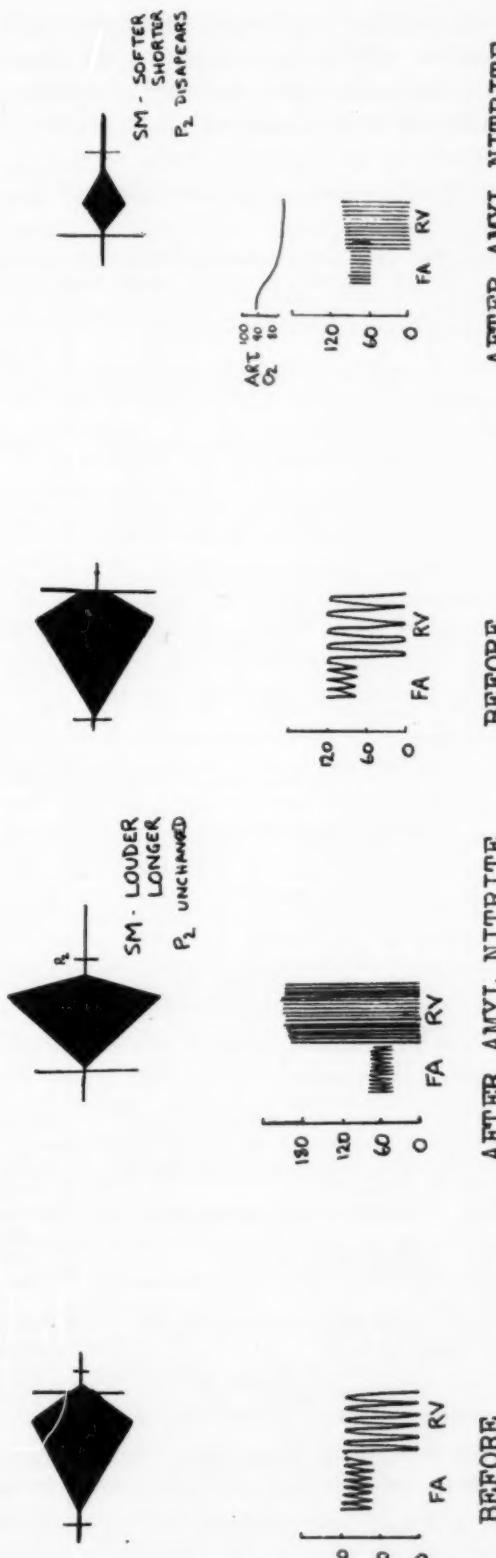
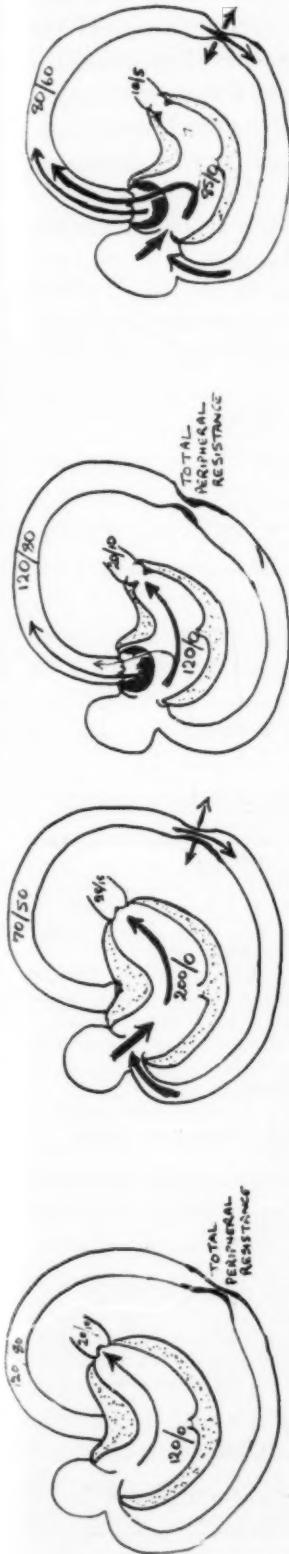


Fig. 7.

Fig. 7.—Moderate pulmonary stenosis. Before amyl nitrite, the length of murmur, width of splitting, and similar systemic and right ventricular systolic pressures are indistinguishable from those of mild Fallot's tetralogy. Amyl nitrite suddenly releases the peripheral resistance, causing a drop in systemic pressure and an increased venous return to the right heart. The marked increase in right ventricular pressure and loudness of murmur proves that the ventricular septum is intact.

Fig. 8.—Mild tetralogy. Pre-amyl nitrite phonocardiogram and pressure data are indistinguishable from those of moderate pulmonary or infundibular stenosis. However, amyl nitrite reduces both systemic and right ventricular pressures, proving the presence of a large ventricular septal defect. The drop in arterial oxygen saturation reflects the increased venoarterial shunt through the defect, while the softer and shorter murmur indicates the fall in pulmonary flow.

for a given degree of stenosis, pulmonary blood flow and, hence, the length and loudness of the murmur will be influenced by the systemic resistance. If the systemic resistance is high, the right ventricular systolic pressure rises, resulting in increased pulmonary flow, as shown by the favorable effect of systemic hypertension¹⁶ and coarctation of the aorta^{1,3} on the tetralogy. If systemic resistance falls, the right ventricular pressure should likewise fall, resulting in decreased

TABLE II. THE DIFFERENTIAL DIAGNOSIS BETWEEN MILD FALLOT'S TETRALOGY AND MODERATELY SEVERE PULMONARY OR INFUNDIBULAR STENOSIS

	MILD OR ACYANOTIC TETRALOGY	PULMONARY OR INFUNDIBULAR STENOSIS (MODERATELY SEVERE)
Symptoms	Nil or mild dyspnea (squatting usually absent)	Usually none
Cyanosis (ear oximetry)	May be absent at rest; brought out by effort, or amyl nitrite	Absent
Hemoglobin	Normal or slightly elevated	Normal
Clubbing	Absent or slight	Absent
"A" Wave	Normal	Often normal; may be dominant
Heart Size	Normal	Normal
RV Lift	Slight	Slight to moderate
Systolic Murmur Before	Loud; fills systole; A ₂ not obscured	Loud; fills systole; A ₂ partially obscured
After amyl nitrite	Softer and shorter	Louder and longer
Heart Sounds Before	Usually single; soft P ₂ may be heard in PA; split always wide (average, 0.09 sec.)	P ₂ soft in PA; split always wide (average, 0.08 sec.)
After amyl nitrite	Loud first; A ₂ softer; P ₂ disappears	Loud first; A ₂ softer or hidden; P ₂ remains
ECG	RV hypertrophy (moderate)	RV hypertrophy (moderate)
X-Ray	Lung fields normal or slightly oligemic Shape: sabot or normal Right aorta helpful	Lung fields normal or slightly oligemic Poststenotic dilatation if valvular stenosis, but absent if infundibular stenosis
Cardiac Catheterization Before	Pulmonary or infundibular stenosis Systemic systolic = RV systolic	Pulmonary or infundibular stenosis Systemic systolic = RV systolic
After amyl nitrite	Systemic and RV fall	Systemic falls ++; RV rises ++
Other Methods Aorta entered from RV Selective angiography from RV Dye Dilution	Conclusive if succeeds Aorta filled Aorta filled from RV	Excludes Aorta not filled No filling of aorta from RV

pulmonary flow with shortening and softening of the murmur. Amyl nitrite was thus chosen as an agent which would selectively reduce the systemic resistance while subjecting the right ventricle to increased work. By such a circulatory manipulation the presence or absence of a ventricular septal defect can be readily detected.

The striking feature in the tetralogy was the fact that the right ventricular pressure fell despite the greatly increased venous return following the inhalation of amyl nitrite. This must imply the presence of a large ventricular septal defect capable of offering an effective escape route and permitting the right ventricular pressure to fall in response to the lowered systemic resistance (Fig. 8). It might be anticipated that cases of tetralogy with relatively small ventricular septal defects should show no fall, or even a rise in right ventricular pressure. So far no such case has been encountered. In the tetralogy the fall in systemic pressure was not so marked or so prolonged as in pulmonary stenosis with intact ventricular septum. This is attributed to the quicker adjustment of systemic arterial and venous blood volumes that must occur when there is a wide communication in the heart (Figs. 1 and 8). The increased venoarterial shunt during inhalation of amyl nitrite resulted in increased cyanosis, which was confirmed by oximetry. The fall in systemic resistance and, hence, in right ventricular pressure must reduce the gradient across the stenosis and result in a fall-off in pulmonary flow. In addition, pulmonary flow will also be handicapped by greater stroke volume lost down the aorta because of the fall in systemic diastolic pressure. This may account for the fact that marked shortening and softening of the systolic murmur sometimes occurred despite little fall in systemic systolic pressure.

It is believed that the transient reduction in blood flow through the stenosed outflow tract accounts for the reduction in the intensity and duration of the systolic murmur during the inhalation of amyl nitrite in all cases of tetralogy, whether extreme or mild (Figs. 4 and 5). In mild cases with the murmur loud at the aortic sound the murmur shortens so considerably that it ends before the sound, or obscures much less of it (Fig. 5). In severe cases the murmur shortens even more and not infrequently disappears, sometimes leaving only an aortic ejection sound^{1-3,11,12} in its place (Fig. 4). The temporary disappearance of the pulmonary second sound in those mild cases in which it was recorded (Fig. 5) reflects the fall in pulmonary diastolic pressure that must accompany reduced pulmonary flow. As the systemic resistance rises with the wearing off of the effect of amyl nitrite, so the improving pressure gradient and pulmonary flow are revealed by a gradual increase in length and loudness of the murmur.

The chief application of these observations is in the diagnosis of mild or acyanotic cases of tetralogy from moderately severe cases of pulmonary stenosis. Both present many similar features (Table II). Thus, common to both are good effort tolerance, absence of squatting, absence of cyanosis at rest, a loud systolic murmur extending into the aortic component but not obscuring it and wide splitting of the second sound with a soft, delayed pulmonary component, right ventricular hypertrophy on electrocardiogram, similar radiologic appearances, and, at cardiac catheterization, similar systemic and right ventricular systolic pressures. Points favoring a mild tetralogy may be slight cyanosis during effort,

which if not visible is usually readily revealed by ear oximetry, and a mild polycythemia associated with minimal clubbing. Cyanosis due to a right-to-left interatrial shunt usually occurs only in severe cases of pulmonary stenosis in which the murmur is so prolonged as to render the diagnosis reasonably straightforward.¹ The diagnosis appears to depend on the awareness that cases of acyanotic tetralogy of Fallot may masquerade as pulmonary stenosis, and hitherto has often required specialized techniques such as selective angiography from the right ventricle, a good prograde angiogram, and selective dye dilution curves to show filling of the aorta from the right ventricle.² However, the use of amyl nitrite can quickly settle the problem either at the bedside or in the laboratory. The test can be repeated without harm to the patient, and phonocardiographic confirmation is useful but not essential. During cardiac catheterization the amyl nitrite test has proved more satisfactory and convenient than the exercise test which we used to employ whenever similar systolic pressures were encountered.

SUMMARY

The effect of the inhalation of amyl nitrite on the systemic and right ventricular pressures and on the systolic murmur and heart sounds has been studied in pulmonary stenosis with intact ventricular septum and Fallot's tetralogy.

In pulmonary or infundibular stenosis with intact ventricular septum the inhalation of amyl nitrite results in a pronounced fall in systemic pressure and a marked rise in right ventricular pressure. The increased right ventricular pressure results in a striking increase in the loudness of the systolic murmur. After cessation of the inhalation, pressures and murmur gradually return to their original state in about 4 minutes.

In Fallot's tetralogy the inhalation of amyl nitrite results in a moderate fall in both the systemic and right ventricular systolic pressures, with an increase in right-to-left shunt. The reduced right ventricular pressure results in a diminution in pulmonary flow, which is reflected by a decrease in the intensity and duration of the systolic murmur. As the effect of the vapor wears off, the pressures, murmur, and cyanosis return to the basal level, usually within 3 to 4 minutes.

The reasons for these striking differences are discussed fully. The effect was similar whether the case of pulmonary stenosis or Fallot's tetralogy was mild, moderate, or severe.

The amyl nitrite test is of value in settling the difficult and important diagnosis of mild (acyanotic) Fallot's tetralogy and moderately severe pulmonary or infundibular stenosis with intact ventricular septum, in cases in which the clinical, electrocardiographic, radiologic, and catheter findings may be identical. The different behavior of the systolic murmur at the bedside and of the pressures during cardiac catheterization readily distinguishes the two conditions.

We wish to thank members of the Staff of Groote Schuur Hospital for referring cases for investigation, and the Superintendent, Dr. J. Burger, for permission to publish. We should like

also to acknowledge the assistance received from our technicians, Mr. and Mrs. L. W. Piller and Mr. P. Flagg, and the help of Sisters J. Abbott and G. Wheeldon, and to thank Mr. Todt for photographic services.

REFERENCES

1. Vogelpoel, L., and Schrire, V.: Circulation **11**:714, 1955.
2. Vogelpoel, L., Schrire, V., Nellen, M., and Goetz, R. H.: Angiology **8**:215, 1957.
3. Vogelpoel, L., and Schrire, V.: Pulmonary Stenosis With Intact Ventricular Septum and Fallot's Tetralogy: Preoperative and Postoperative Assessment of Severity by Auscultation, Abstracts of Communications, p. 232, Third World Congress of Cardiology, Brussels, 1958. (In press.)
4. Vogelpoel, L., Schrire, V., Nellen, M., and Swanepoel, A.: South African M. J. **32**:877, 1958.
5. Schrire, V., and Vogelpoel, L.: Am. HEART J. **49**:162, 1955.
6. Wood, P.: Brit. Heart J. **20**:282, 1958.
7. McCord, M. C., Van Elk, J., and Blount, S. G., Jr.: Circulation **16**:736, 1957.
8. Soulié, P., Joly, F., Carlotti, J., and Sicot, J.-R.: Arch. mal. coeur **44**:577, 1951.
9. Brock, R. C., and Campbell, M.: Brit. Heart J. **12**:403, 1950.
10. Brock, R.: The Anatomy of Congenital Pulmonary Stenosis, London, 1957, Cassell and Company, Ltd.
11. Leatham, A., and Vogelpoel, L.: Brit. Heart J. **16**:21, 1954.
12. Nellen, M., Vogelpoel, L., and Schrire, V.: Aortic Ejection Sound, Abstracts of Communications, p. 440, Third World Congress of Cardiology, Brussels, 1958.
13. Wood, P.: Diseases of the Heart and Circulation, Ed. 2, London, 1956, Eyre & Spottiswoode.
14. Vogelpoel, L., Schrire, V., Nellen, M., and Swanepoel, A.: The Value of Amyl Nitrite in the Diagnosis of Systolic Murmurs. (In preparation.)
15. Barlow, J., and Shillingford, J.: Brit. Heart J. **20**:162, 1958.
16. Hamilton, W. F., Winslow, J. A., and Hamilton, W. F., Jr.: J. Clin. Invest. **29**:20, 1950.
17. Schrire, V., and Phillips, W.: South African M. J. **32**:232, 1958.
18. Lowe, J. B.: Pulmonary Stenosis and Ventricular Septal Defect, Abstracts of Communications, p. 228, Third World Congress of Cardiology, Brussels, 1958.

The Mean Ventricular Axis in Congenital Heart Disease: A Study Considering the Natural Incidence of the Malformations

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Recently, Sodi-Pallares and collaborators¹ have stressed the importance of the mean manifest electrical axis of the ventricular activation process ($\bar{A}QRS$) in the differential diagnosis of congenital heart diseases. They divided the frontal plane into 6 parts, according to Bayley's triaxial system, thus analyzing the distribution of 16 congenital malformations from 60 to 60 degrees.

The importance of such a study is beyond any discussion, and the value of the determination of $\bar{A}QRS$ in the diagnosis of congenital heart diseases has been extensively proved by our daily experience. However, it called our attention to the fact that the incidence of the lesions observed in their series does not correspond to the approximate "natural incidence"[†] of the different types of malformations in the whole group of congenital heart diseases. For instance, they found a high incidence of tetralogy of Fallot and tricuspid atresia as compared to a relatively low incidence of ventricular septal defect and pure pulmonic stenosis. Thus, we feel that the results obtained by Sodi-Pallares and co-workers are biased, since their study was based only on cases in which electrocardiograms were available.

In order to appreciate the results that would be obtained if the approximate natural incidence was considered, we performed a careful analysis of the findings in the paper referred to above, and carried out a study of our own on the distribution of the mean ventricular axis in patients with congenital cardiac anomalies.

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[†]We call "natural incidence" that which could be obtained from the statistical studies of different authors, based on confirmed anatomic diagnosis (by surgery or autopsy).

MATERIAL AND METHODS

The electrocardiograms of 877 patients with congenital heart disease were analyzed. The types of malformations selected were the same as those studied by Sodi-Pallares and associates (Table I). The majority of the cases were from the files of the Cardiovascular Laboratories of St. Vincent Charity Hospital and Cleveland Clinic. A few of the tracings were reviewed from the medical literature.²⁻²⁰

TABLE I. NUMBER OF CASES IN OUR SERIES

MALFORMATION	NUMBER OF CASES	PER CENT
Pulmonic stenosis	120	13.7
Atrial septal defect	114	13.0
Ventricular septal defect	102	11.6
Patent ductus arteriosus	87	9.9
Tricuspid atresia	85	9.7
Tetralogy of Fallot	66	7.5
Transposition	49	5.6
Coarctation	47	5.3
Aortic stenosis	45	5.1
Ebstein's disease	44	5.0
Persistent common atrioventricular canal	40	4.5
Trilogy of Fallot	19	2.1
Single ventricle	17	1.9
Eisenmenger's complex	16	1.8
Truncus arteriosus	15	1.7
Pentalogy of Fallot	11	1.2
Total	877	

All of the cases selected had a hemodynamic diagnosis, and in most the diagnosis was proved either by surgery or autopsy. The $\bar{A}QRS$ was calculated by measuring the areas inclosed by the QRS complex of the three standard leads. These areas are expressed in microvolt-second (mvs).²¹ Each mvs corresponds to a surface measuring 1 mm. in height and 0.01 second in duration. Four mvs is equal to one Ashmann unit. In each case the value of the positive and negative areas of the QRS complex in Leads I, II, III were summed up algebraically. Arbitrary relative values were then used to express the results of this algebraic summation and plotted in the positive or negative portion of each lead according to the algebraic sign.

Let us suppose for instance that the net areas of the QRS complex in Leads I, II, and III were found to be: +8.0, and -8 mvs, respectively. Considering 1 mvs to be equal to 1 cm., we shall have: +8 cm. for Lead I, 0 cm. for Lead II, and -8 cm. for Lead III (Fig. 1).

From the points plotted in each lead, as is shown in Fig. 1, perpendiculars are dropped and a line is drawn from the center of the graph to the point at which they intersect. Such a line represents the accurate location of the $\bar{A}QRS$ in the frontal plane.

The frontal plane was subdivided into 12 segments (30 degrees each), and the distribution of the mean ventricular axes was analyzed on these segments. The percentual incidence of each particular malformation in each segment was then calculated according to the location of the $\bar{A}QRS$, by computing the total number of cases of all the lesions found in that particular segment (Table II).

This incidence was then corrected by comparing the percentages obtained with the natural incidence of each malformation in the whole group of congenital heart diseases (Table III). This approximate natural incidence was calculated by comparing the statistical studies of different authors²²⁻²⁵ with the ones obtained from our own files (a total of over 3,000 cases). Actually, in the determination of the natural incidence we have considered the whole group of congenital heart diseases as comprised only of the 16 malformations analyzed in this paper. We did so in order to keep the same cases studied by Sodi-Pallares,¹ thus permitting a better comparative analysis.

The correct incidence of each lesion per segment was calculated as follows:
Number of cases of each lesion in the segment

× Natural Incidence

The incidence in our series

The results obtained for each lesion in the segment were then transformed into percentual values. For example, in our Segment II we had: tricuspid atresia, 28 cases; persistent common atrioventricular canal, 9 cases; and single ventricle, 3 cases. By applying the aforementioned formula we obtained: tricuspid atresia, 8.65; persistent common atrioventricular canal, 8.00; and single ventricle, 1.56. By adding these figures we have a total of 18.21. In order to transform these results into percentual values, we did as follows:

$$\text{Tricuspid atresia} = \frac{8.65 \times 100}{18.21} = 46.96\%$$

$$\text{P.C.A.V.C.} = \frac{8 \times 100}{18.21} = 44.73\%$$

TABLE II. PERCENTUAL DISTRIBUTION OF EACH MALFORMATION PER SEGMENT

Segment I		Segment VII		Segment X	
Tricuspid atresia	71.42	I.A.S.D.	35.00	P.D.A.	29.31
I.V.S.D.	14.28	Tetralogy of Fallot	20.80	I.V.S.D.	16.54
Pulmonic stenosis	7.14	Pulmonic stenosis	18.20	Aortic stenosis	12.03
P.C.A.V.C.	4.76	Transposition	9.10	Pulmonic stenosis	9.78
Single ventricle	2.38	I.V.S.D.	6.50	Coarctation of aorta	9.78
		Trilogy of Fallot	6.50	I.A.S.D.	6.77
		Ebstein's disease	1.30	Transposition	5.26
		Pentalogy of Fallot	1.30	Tricuspid atresia	5.26
		Eisenmenger's complex	1.30	Tetralogy of Fallot	2.26
				Ebstein's disease	2.26
				Truncus arteriosus	0.75
Segment II		Segment VIII		Segment XI	
Tricuspid atresia	70.0	I.A.S.D.	20.25	P.D.A.	27.90
P.C.A.V.C.	22.5	Pulmonic stenosis	15.73	Coarctation of aorta	19.76
Single ventricle	7.5	Tetralogy of Fallot	15.17	I.V.S.D.	18.60
		Ebstein's disease	15.16	Aortic stenosis	17.44
		Transposition	10.69	I.A.S.D.	5.82
		I.V.S.D.	7.29	Pulmonic stenosis	4.66
		Eisenmenger's complex	5.05	Tricuspid atresia	4.66
		Pentalogy of Fallot	3.37	Tetralogy of Fallot	1.16
		Coarctation of aorta	2.81		
		Truncus arteriosus	2.24		
		Trilogy of Fallot	1.68		
		Aortic stenosis	0.56		
Segment III		Segment IX		Segment XII	
P.C.A.V.C.	45.92	Pulmonic stenosis	23.38	I.V.S.D.	42.86
Single ventricle	27.01	I.A.S.D.	15.19	Tricuspid atresia	28.58
Tricuspid atresia	20.80	P.D.A.	9.88	Pulmonic stenosis	9.52
I.V.S.D.	6.27	I.V.S.D.	9.44	I.A.S.D.	9.52
		Tetralogy of Fallot	7.62	Coarctation of aorta	4.76
		Transposition	6.75		
		Aortic stenosis	5.84		
		Coarctation of aorta	4.94		
		Ebstein's disease	4.94		
		Truncus arteriosus	4.49		
		Trilogy of Fallot	3.14		
		Eisenmenger's complex	2.69		
		Pentalogy of Fallot	1.70		
Segment VI					
Pulmonic stenosis	23.08				
I.V.S.D.	15.38				
I.A.S.D.	15.38				
Tetralogy of Fallot	15.38				
Trilogy of Fallot	15.38				
Transposition	7.70				
Ebstein's disease	7.70				

I.V.S.D.—Interventricular septal defect. P.C.A.V.C.—Persistent common atrioventricular canal.
I.A.S.D.—Interatrial septal defect. P.D.A.—Patent ductus arteriosus.

$$\text{Single ventricle} = \frac{1.56 \times 100}{18.21} = 8.35\%$$

Obviously, as with any statistical study of this nature, ours is not perfect. However, we feel that it can furnish satisfactory data to be applied as factors of correction, thus leading us as close as possible to reality, as far as the law of probabilities is concerned.

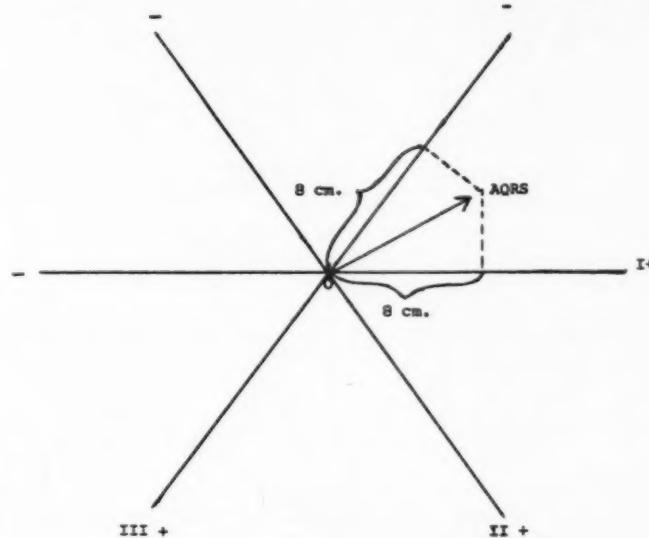


Fig. 1.—Illustration of the method of calculating the ΔQRS from the standard leads.

TABLE III. NATURAL INCIDENCE OF CONGENITAL HEART DISEASE

MALFORMATION	PER CENT
Atrial septal defect	20.0
Ventricular septal defect	17.0
Pulmonic stenosis	15.0
Patent ductus arteriosus	13.0
Tetralogy of Fallot	10.0
Coarctation	7.0
Persistent common atrioventricular canal	4.0
Transposition	3.0
Tricuspid atresia	3.0
Trilogy of Fallot	2.5
Truncus arteriosus	1.5
Aortic stenosis	1.0
Ebstein's disease	1.0
Single ventricle	1.0
Eisenmenger's complex	0.5
Pentalogy of Fallot	0.5

RESULTS

After applying the approximate natural incidence of each malformation for correcting the percentual incidence in each segment, we found the results which are shown in Table IV.

DISCUSSION

It is our opinion that if one divides the frontal plane into 12 segments instead of 6, thus analyzing the distribution of the Δ QRS from 30 to 30 degrees, such a division permits a more nearly accurate differential diagnosis. In the same way, if one corrects the percentual incidence of any lesion in each segment by the approximate natural incidence of this particular lesion, one approaches a more nearly accurate statistical reality.

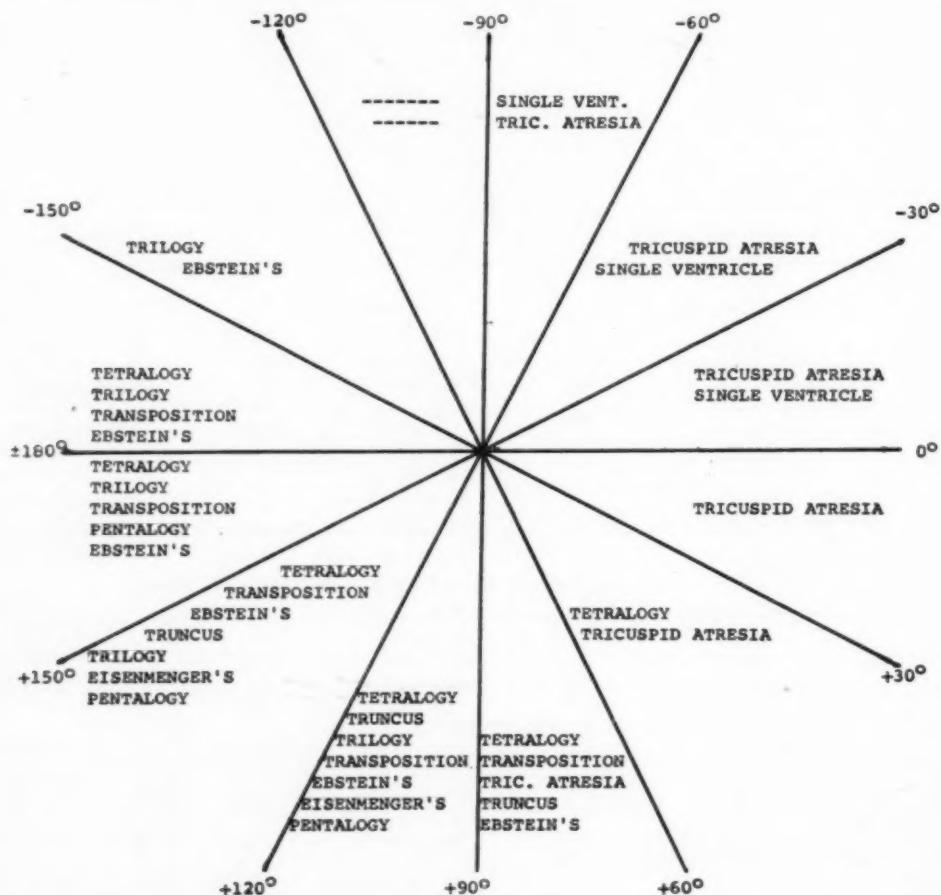


Fig. 2.—Distribution of the cyanotic malformations of our series in the 12 segments of the frontal plane.

We stressed at the beginning of this paper that the results obtained by Sodi-Pallares ought to be more nearly correct statistically, for the reasons we have already pointed out. The following example will demonstrate our point: In the fifth sextant of their classification they found 98 cases of tetralogy of Fallot and 59 cases of pulmonic stenosis. The 98 cases of tetralogy represented 34.51 per cent of the total number of patients with this malformation, and the 59 cases of pulmonic stenosis represented 59.61 per cent of the total number of patients showing this lesion. When they determined the incidence of these two diseases in this sextant, by computing the total number of cases of all the lesions which

had their mean axes plotted on this zone, they found that tetralogy of Fallot represented 16.0 per cent of all these lesions, while pulmonic stenosis represented only 9.6 per cent. Thus, in the table showing the incidence of malformations per segment, tetralogy is classified ahead of pulmonic stenosis in the fifth sextant of Bayley. This, of course, leads one to conclude that whenever a mean ventricular axis is found in this sextant, one should think of tetralogy of Fallot rather than pulmonic stenosis as being the more probable disease. Such a conclusion would be correct if the percentual incidence of these two lesions in their series

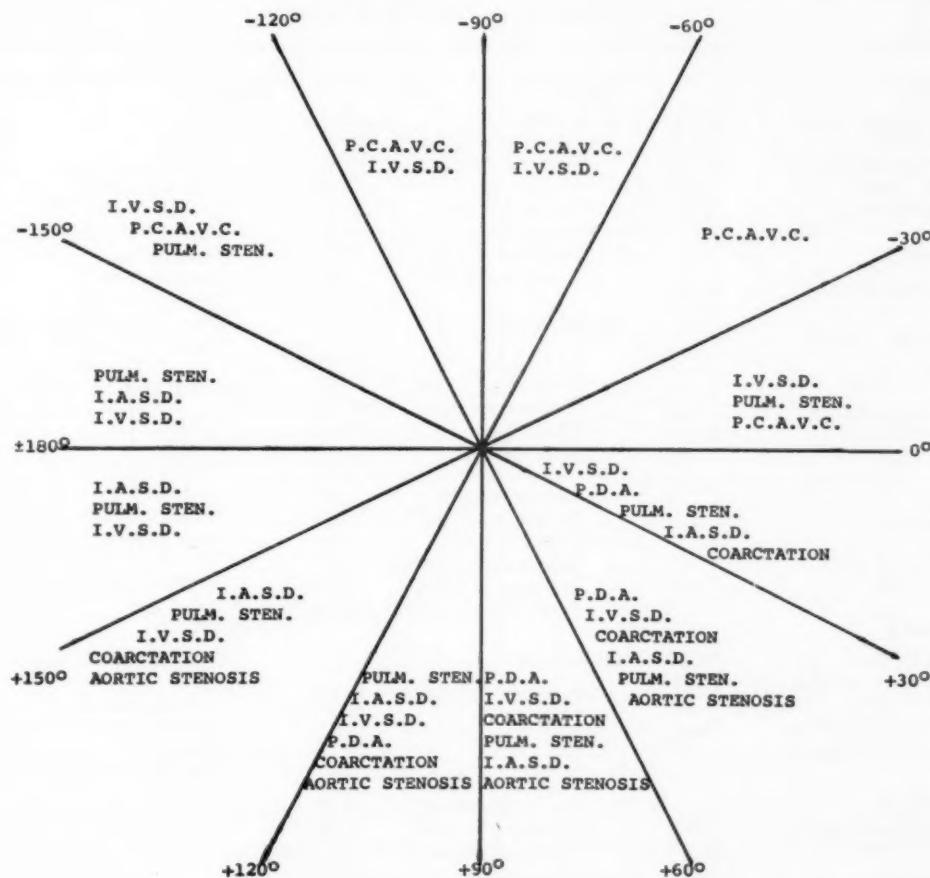


Fig. 3.—Distribution of the acyanotic malformations of our series in the 12 segments of the frontal plane.

would correspond to the real incidence of pulmonic stenosis and tetralogy of Fallot in the whole group of congenital heart diseases. If we correct the above data by the approximate natural incidence of each lesion, we will have different results, so that pulmonic stenosis actually will appear ahead of tetralogy of Fallot (Table V).

Like Sodi-Pallares,¹ we definitely believe that the determination of the mean ventricular axis gives us important clues for the identification of the type of the malformation. We have applied the results we described in Table IV to patients who came to us in the past few months for differential diagnosis of their congenital

lesion. We have noticed that in many instances the possibilities suggested by the location of the QRS correspond to the final surgical or pathologic diagnosis. Of course, this is only one step. As was stressed by Sodi-Pallares,¹ other factors, such as the presence or absence of cyanosis and a careful analysis of the morphology of the tracing, are extremely important and lead us to the exact diagnosis in the majority of the cases. Figs. 2 and 3 show the distribution of the cyanotic and acyanotic malformations of our series in the 12 segments.

TABLE IV. PERCENTUAL DISTRIBUTION OF EACH MALFORMATION PER SEGMENT CORRECTED BY THE APPROXIMATE NATURAL INCIDENCE

Segment I		Segment VII		Segment X	
Tricuspid atresia	39.32	I.A.S.D.	43.21	P.D.A.	35.82
I.V.S.D.	37.17	Tetralogy of Fallot	22.24	I.V.S.D.	22.55
Pulmonic stenosis	13.93	Pulmonic stenosis	15.98	Coarctation of aorta	11.85
P.C.A.V.C.	7.43	I.V.S.D.	7.65	Pulmonic stenosis	9.95
Single ventricle	2.15	Trilogy of Fallot	6.05	I.A.S.D.	9.62
		Transposition	3.96	Tetralogy of Fallot	2.77
Segment II		Pentalogy of Fallot	0.41	Transposition	2.64
Tricuspid atresia	46.92	Ebstein's disease	0.29	Aortic stenosis	2.21
P.C.A.V.C.	44.73			Tricuspid atresia	1.54
Single ventricle	8.35	Segment VIII		Truncus arteriosus	0.62
		I.A.S.D.	31.56	Ebstein's disease	0.43
Segment III		Tetralogy of Fallot	20.57	Segment XI	
Single ventricle	71.42	Pulmonic stenosis	17.53	P.D.A.	33.21
P.C.A.V.C.	20.61	I.V.S.D.	10.88	I.V.S.D.	24.78
I.V.S.D.	4.67	Transposition	5.83	Coarctation of aorta	23.37
Tricuspid atresia	3.30	Coarctation of aorta	3.72	I.A.S.D.	8.26
		Ebstein's disease	3.07	Pulmonic stenosis	4.63
Segment IV		Truncus arteriosus	2.01	Aortic stenosis	3.06
P.C.A.V.C.	60.25	Trilogy of Fallot	1.96	Tetralogy of Fallot	1.39
I.V.S.D.	39.75	Eisenmenger's complex	1.41	Tricuspid atresia	1.30
		Pentalogy of Fallot	1.36		
Segment V		Aortic stenosis	0.10	Segment XII	
I.V.S.D.	44.28	Segment IX		I.V.S.D.	58.11
Trilogy of Fallot	23.76	Pulmonic stenosis	24.01	P.D.A.	11.60
P.C.A.V.C.	18.07	I.A.S.D.	21.01	Pulmonic stenosis	9.65
Pulmonic stenosis	11.19	I.V.S.D.	12.95	Tricuspid atresia	8.17
Ebstein's disease	2.70	P.D.A.	12.06	I.A.S.D.	6.74
		Tetralogy of Fallot	9.44	Coarctation of aorta	5.73
Segment VI		Coarctation of aorta	5.99		
Pulmonic stenosis	21.87	Truncus arteriosus	3.68		
I.A.S.D.	20.11	Trilogy of Fallot	3.39		
I.V.S.D.	19.52	Transposition	3.39		
Tetralogy of Fallot	17.75	Ebstein's disease	1.66		
Trilogy of Fallot	15.37	Aortic stenosis	1.06		
Transposition	3.51	Eisenmenger's complex	0.70		
Ebstein's disease	1.87	Pentalogy of Fallot	0.66		

I.V.S.D.—Interventricular septal defect. P.C.A.V.C.—Persistent common atrioventricular canal.
I.A.S.D.—Interatrial septal defect. P.D.A.—Patent ductus arteriosus.

In their study, Sodi-Pallares and associates¹ placed persistent common atrioventricular canal in the cyanotic group, and Eisenmenger's complex in the acyanotic group. We do not agree with this classification, since all our cases of persistent common atrioventricular canal were acyanotic, while in all patients with

Eisenmenger's complex whom we have seen, cyanosis was present either clinically (detected by physical examination) or subclinically (revealed by the existence of systemic arterial desaturation). It is true that in a few cases of Eisenmenger's complex, cyanosis may be absent in the early stages. However, in most of the patients the changes in the small pulmonary vessels develop during the first years of life, thus producing early systemic desaturation and cyanosis.

We shall not describe the morphology of each one of the malformations in our series, since that was excellently done by Sodi-Pallares.¹

TABLE V

TYPE OF MALFORMATION	SEXTANTS OF BAYLEY		PERCENTUAL DISTRIBUTION CORRECTED BY THE APPROXIMATE NATURAL INCIDENCE OF EACH LESION
	NUMBER OF CASES	PERCENTUAL DISTRIBUTION AS CALCULATED BY SODI-PALLARES	
Patent ductus arteriosus	139	22.6	16.72
Atrial septal defect	113	18.4	26.70
Tetralogy of Fallot	98	16.0	6.62
Coarctation of aorta	65	10.6	6.43
Pulmonic stenosis	59	9.6	17.12
Trilogy of Fallot	44	7.1	1.95
Ventricular septal defect	39	6.3	16.06
Ebstein's disease	18	2.9	0.68
Aortic stenosis	13	2.1	1.07
Transposition	7	1.1	2.88
Eisenmenger's complex	6	0.9	0.36
Truncus arteriosus	5	0.8	1.59
Tricuspid atresia	3	0.5	0.19
Persistent common atrioventricular canal	3	0.5	0.75
Single ventricle	2	0.3	0.25
Pentalogy of Fallot	2	0.3	0.63

CONCLUSION AND SUMMARY

An analysis of the distribution of the Δ QRS in 877 patients with congenital heart disease was performed. The frontal plane was subdivided into 12 segments, and the incidence of each malformation per segment was determined. A correction of the incidence of each lesion was then obtained by means of constants which represent the approximate natural incidence of each one of the malformations in the whole group of congenital heart diseases. The reasons for such a correction are discussed.

The authors stress that the main diagnosis of the anomaly can be established in a great number of cases if the location of the Δ QRS, the existence of cyanosis, and a careful interpretation of the morphology of the tracing are considered.

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REFERENCES

1. Sodi-Pallares, D., Pileggi, F., Cisneros, F., Ginefra, P., Portillo, B., Medrano, G. A., and Bisteni, A.: *AM. HEART J.* **55**:681, 1958.
2. Benchimol, A. B., Anache, M., and Carneiro, R. D.: Persistencia do canal atrioventricular comun, *Arq. bras. cardiol.* **10**:283, 1957.
3. Brown, J. W., Heath, D., and Whitaker, W.: *Am. J. Med.* **20**:322, 1956.
4. Martins de Oliveira, J., and Zimmerman, H. A.: *AM. HEART J.* **55**:369, 1958.
5. Toscano-Barbosa, E., Brandenburg, R. O., and Burchell, H. B.: *Proc. Staff. Meet. Mayo Clin.* **31**:513, 1956.
6. Van Lingen, B., and Bauersfeld, S. R.: *AM. HEART J.* **50**:13, 1955.
7. Gotzsche, H., and Falholt, W.: *AM. HEART J.* **47**:587, 1954.
8. Kossmann, C. E.: *Advances in Electrocardiography*, New York, 1958, Grune & Stratton, Inc.
9. Nadas, A. S.: *Pediatric Cardiology*, Philadelphia, 1957, W. B. Saunders Company.
10. Barbosa, A., Tranches, J., Sawaya, N., Timover, M., Adachi, T., Fujioka, T., and Décourt, L. V.: Anomalia de Ebstein, *Rev. Hosp. clínicas* **12**:352, 1957.
11. Neill, C. A., and Brink, A. J.: *Circulation* **12**:612, 1955.
12. Espino-Vela, J., Chavez-Fraga, O., Ordonez, F. G., and Calvo, A. M.: *Arch. Inst. cardiol. Mexico* **26**:67, 1956.
13. Marsico, F., Peñaloza, D., Tranches, J., Limon, R., and Sodi-Pallares, D.: *AM. HEART J.* **49**:188, 1955.
14. Macia, E. R., Espino-Vela, J., Rubio, A. V., Fishleder, B. L., and Castro Abren, D.: *Arch. Inst. cardiol Mexico* **26**:498, 1956.
15. Goodwin, J. F., Wynn, A., and Steiner, R. E.: *AM. HEART J.* **45**:144, 1953.
16. Iriarte, M., Rodrigues, R., Espino-Vela, J., and Rubio, A. V.: *Arch. Inst. cardiol. Mexico* **27**:581, 1957.
17. Espino-Vela, J., Mendez-Aponte, J., Aguilar, C., Portillo, B., Pinzon, J., Quiroga, R., and Rubio, V.: *Arch. Inst. cardiol. Mexico* **28**:174, 1958.
18. Rogers, H. M., and Rudolph, C. C.: *AM. HEART J.* **45**:623, 1953.
19. Azevedo, A. de C., Netoo, M. B., Carvalho, A. A., Roubach, R., Toledo, A. N., and Garcia, A.: *AM. HEART J.* **49**:288, 1955.
20. Cabrera, E., Campos, C. de M., and Fernandez, J. C.: *Arch. Inst. cardiol. Mexico* **22**:151, 1952.
21. Bayley, R. H.: Referred to by Sodi-Pallares, D., and Calder, R. M.: *New Bases of Electrocardiography*, St. Louis, 1956, The C. V. Mosby Co.
22. Keith, J. D., Rowe, R. D., and Vlad, P.: *Heart Disease in Infancy and Childhood*, New York, 1958, The Macmillan Co.
23. Ober, W. B., and Moore, T. E., Jr.: Congenital Cardiac Malformations in the Neonatal Period: An Autopsy Study, *New England J. Med.* **253**:271, 1955.
24. Warburg, E.: Clinical Statistics of Congenital Cardiac Disease: 1,000 Cases Analyzed. Preliminary Report, *Acta med. Scandinav.* **151**:209, 1955.
25. Gibson, S., and Clifton, W. M.: Congenital Heart Disease: A Clinical and Postmortem Study of 105 Cases, *Am. J. Dis. Child.* **55**:761, 1938.

Recurrent Ventricular Tachycardia as the Chief Manifestation of Myocarditis of Unknown Etiology

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Prolonged and/or repetitive ventricular tachycardia has been observed in heart disease of varied etiology, such as atherosclerotic coronary artery disease, rheumatic heart disease, and congenital heart disease. An occasional instance has been reported in which no evidence of organic disease was present. Although supraventricular cardiac arrhythmias, conduction defects, and premature ventricular contractions are commonly observed in myocarditis, only a few well-documented cases of ventricular tachycardia have been observed in myocarditis of known etiology. In myocarditis of unknown etiology (so-called "isolated myocarditis"), ventricular tachycardia has been mentioned but rarely. Myocarditis of unknown etiology usually manifests itself as progressive intractable cardiac failure and/or relatively sudden death. A case is reported in which repetitive ventricular tachycardia observed over a period of 10 months was the chief manifestation of a fatal case of myocarditis of unknown etiology.

CASE REPORT

A 19-year-old white man, an airman on duty in Newfoundland, first noted the onset of hard rapid beating of his heart about 10 months prior to his admission to Walter Reed Army Hospital. The initial episode lasted 6 to 8 hours, and was complicated by mild epigastric pain. By the time he reported on sick call only his subsiding epigastric pain was present. Thereafter, he had numerous instances (approximately 15 or 16) of tachycardia lasting from a few minutes to several hours, and these gradually became more frequent and of longer duration. These episodes usually occurred after eating or after walking, or with fatigue, but occasionally occurred spontaneously without any known precipitating cause. Between episodes he noted frequent premature contractions. On May 27, 1956 (6 months after onset), an attack persisted for 5 hours, the arrhythmia was recorded electrocardiographically for the first time, and he was admitted to his base hospital.

The arrhythmia continued after this first admission and failed to respond to sedation, but converted to sinus rhythm in 24 hours after he was given oral quinidine sulfate. An electrocardiogram taken after the arrhythmia subsided showed frequent multifocal premature ventricular contractions and inverted T waves in the medial precordial leads.

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A general physical examination, including cardiac examination, on the first hospital admission revealed normal findings except for the tachycardia. Laboratory studies, including a complete blood count, erythrocyte sedimentation rate, urinalysis, serology, and serum cholesterol, were normal. A chest roentgenogram recorded on June 5, 1956, was compared with a roentgenogram taken on Nov. 5, 1955, and both were considered to be normal. Fluoroscopy of the heart and lungs revealed no abnormalities, apart from frequent premature ventricular contractions. Despite continued therapy with quinidine, he had many short episodes of arrhythmia, including one which lasted 48 hours. During this latter episode his heart rate varied from 150 to 250 beats per minute. Frank congestive heart failure and dyspnea did not develop, but he was described as pale, apprehensive, frightened, lying perfectly still, refusing to eat or drink. Epigastric distress developed, which may have represented early cardiac failure. This episode finally terminated while he was on intravenous therapy with procaine amide, and he was given a maintenance dosage of 250 mg. three times daily. In addition, he was digitalized with 2 mg. of digoxin in 18 hours, and then was given a maintenance dosage of 0.25 mg. daily for 3 days. However, he continued to have frequent multifocal premature ventricular contractions with runs of coupling.

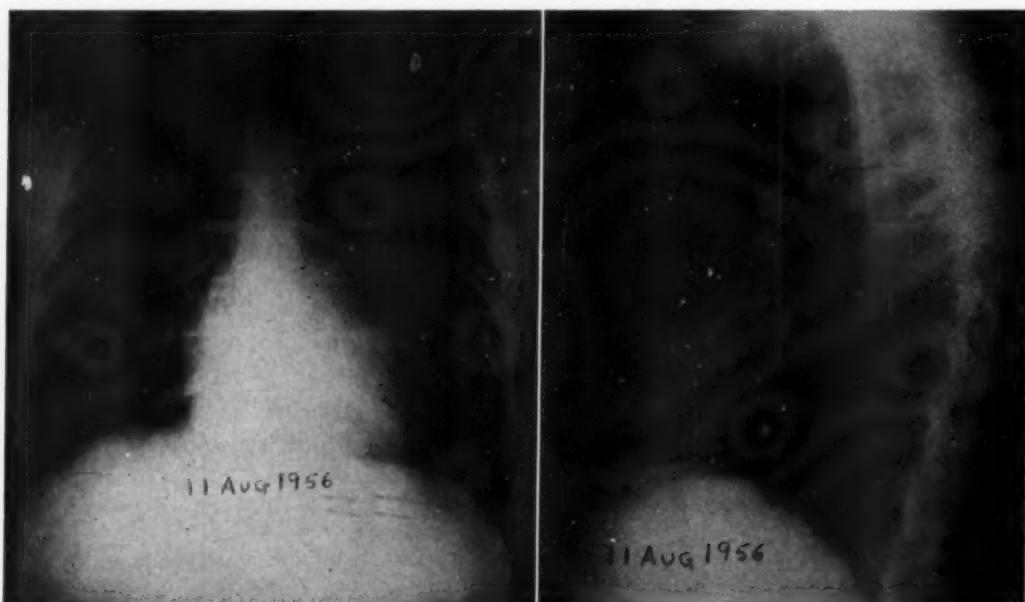


Fig. 1.—Roentgenograms of Aug. 11, 1956. *Left:* Postero-anterior view.
Right: Left lateral view.

Initially, his attending physicians thought that the arrhythmia was supraventricular in nature with aberrant ventricular conduction, but because many of the complexes in the arrhythmia strongly resembled the premature ventricular contractions seen in the electrocardiogram between attacks, and because of the slight irregularity of the rate and the belief that P waves could be seen occurring at a slower rate, it was thought that he had ventricular tachycardia.

On July 28, 1956, he was sent to a stateside hospital where physical examination again was normal, except for frequent premature ventricular contractions. As in the other hospital, repeated episodes of ventricular tachycardia occurred. One episode of ventricular tachycardia failed to respond to 20 ml. of 10 per cent magnesium sulfate intravenously, but converted to a sinus mechanism with runs of trigeminy after 500 mg. of procaine amide had been given intravenously. Oral procaine amide was continued, but was later stopped after the development of bradycardia and a prolonged P-R interval. He was then transferred to Walter Reed Army Hospital, being admitted on Aug. 10, 1956.

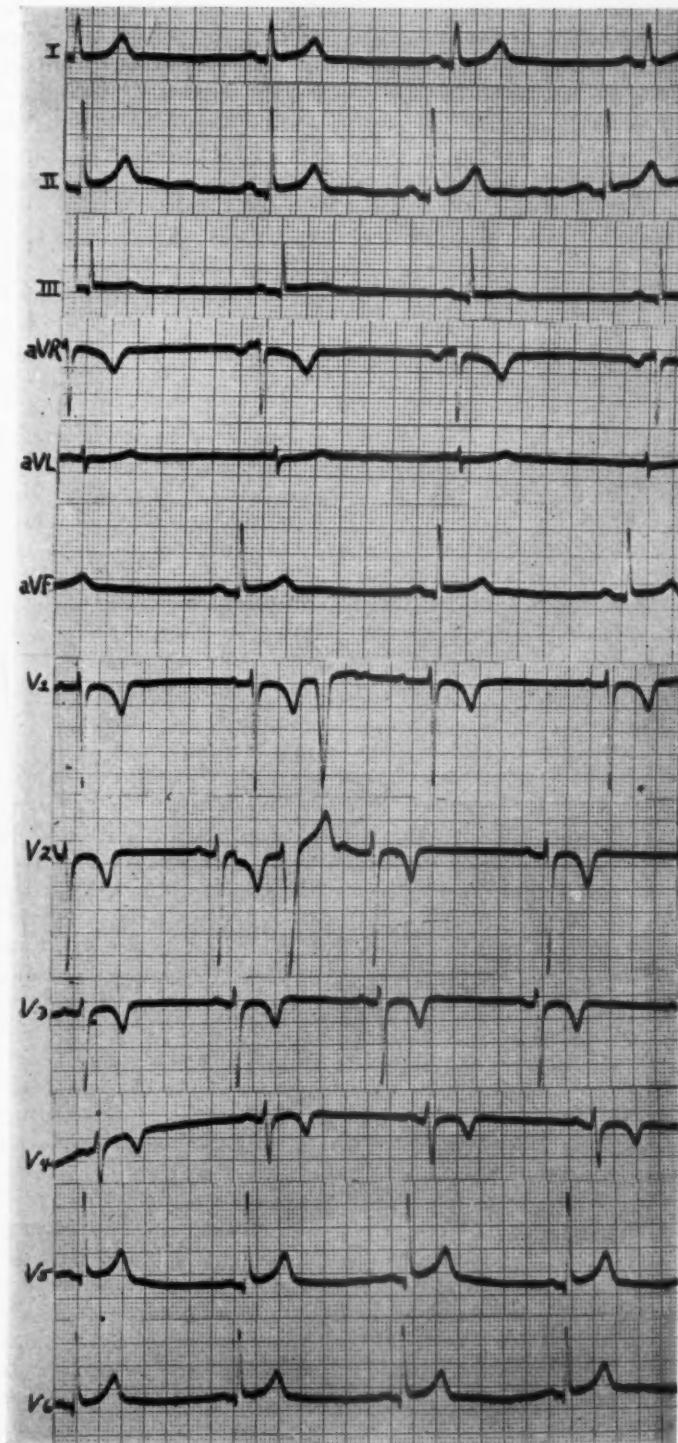


Fig. 2.—Electrocardiogram between episodes of ventricular tachycardia.

Further history elicited from the patient revealed no previous or recent infectious diseases, trauma, exposure to chemicals, or any other significant history. Family history and past medical history were noncontributory.

Physical examination revealed a six-foot, one-inch tall, 180-pound white man in no distress. The pulse was 60, with an occasional to frequent premature ventricular contraction, and the blood pressure was 110/80 mm. Hg. He had severe dental caries, but denied having any dental pain. His lungs were clear to auscultation and percussion. The point of maximum impulse of the heart was in the fifth intercostal space in the left mid-clavicular line. The heart tones were normal. The second pulmonic sound was split but was not accentuated. No cardiac murmurs were heard. The remainder of the physical examination was entirely normal.

Laboratory studies revealed a white blood count of 6,100 per cubic millimeter, and a differential count showed 64 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, and 6 per cent eosinophils. The hemoglobin was 18.2 Gm. per 100 ml. of blood; the hematocrit was 48 per cent; and the corrected erythrocyte sedimentation rate was 3 mm. per hour (Wintrobe). The urinalysis was normal, and serology was negative. Antistreptolysin O-titer was 100 units, and total lipids were 682 and 732 mg. per 100 ml. of blood on two separate occasions. Two basal metabolic rates were -45 and -37, respectively. The protein bound iodine was 7 mcg. per 100 ml. of blood; serum sodium, 138 mEq. per liter; potassium, 4.3 mEq. per liter; chloride, 102 mEq. per liter; carbon dioxide, 29.4 mEq. per liter. Chest roentgenograms (Fig. 1) showed questionable enlargement of the cardiac silhouette when compared with previous roentgenograms. Fluoroscopy of the heart and lungs was normal. An electrocardiogram on admission showed a sinus rhythm with an average rate of 50, a normal P-R interval, multifocal premature ventricular contractions, and T-wave inversion in Leads III, aVF, and V₁ through V₄. Fig. 2 is a representative example of the patient's electrocardiogram between episodes of ventricular tachycardia. Fig. 3 shows several examples of the patient's ventricular tachycardia occurring during the course of his illness.

Course in the Hospital.—During hospitalization this patient was afebrile, and never had chest pain, cyanosis, or congestive heart failure. On the night of admission an episode of ventricular tachycardia recurred. The electrocardiogram taken during this episode was bizarre, with a ventricular rate of 200 per minute. There were irregular complexes and several short runs of normal complexes with interpolated multifocal premature ventricular contractions. He responded temporarily to barbiturate sedation, but the ventricular tachycardia resumed. After the intravenous administration of 700 mg. of procaine amide, normal QRS complexes became more frequent and then predominated, and the ventricular tachycardia became a series of multifocal premature ventricular contractions. The ventricular tachycardia recurred intermittently during the night, and finally subsided spontaneously the following morning. Numerous episodes of ventricular tachycardia, with rates varying from 200 to 280, occurred during hospitalization. Several episodes abated after intramuscular Amytal sodium was administered. Barbiturate sedation, however, had no preventive effect. He was again digitalized with 1.25 mg. of digoxin and was placed on a maintenance dosage of 0.25 mg. three times daily from September 11 to 18. It was discontinued when on September 18, ventricular tachycardia, at rates varying from 200 to 260 per minute, resumed and persisted for 60 hours, despite the use of Amytal sodium, intravenous procaine amide in amounts varying from 300 to 900 mg., 8 mEq. of potassium chloride intravenously (this was discontinued when his rate increased and it was apparent that digoxin toxicity was not a factor), 0.75 mg. of Prostigmin, intravenously, and quinidine gluconate, approximately 200 mg., intravenously. During this time his blood pressure was not obtainable because of the rapid heart rate and cardiac failure, but he remained conscious and alert and remained perfectly still. He refused all food and fluids. His entire chest wall and neck vessels pulsated violently. His extremities were pale, cold and sweaty, and he was apprehensive, restless, and agitated, and at times had hiccups, nausea, and vomiting. Finally, on September 21, his arrhythmia was converted to sinus rhythm by using a combination of 15 mg. of morphine sulfate and 500 to 600 mg. of quinidine gluconate, intravenously.

The use of quinidine gluconate was continued, with 400 mg. being given every 4 hours intramuscularly. On September 22, intramuscular quinidine was stopped and 600 mg. of oral quinidine sulfate every 4 hours was given. This was increased to 800 mg. when long runs of ventricular tachycardia began to recur.

Late in the evening of September 22, he became restless and began to have difficulty in breathing. Ventricular tachycardia had recurred at a rate of 200. Oxygen and Amytal sodium had no effect and his breathing became more irregular. He was given 200 mg. of quinidine gluconate intravenously, but his heart rate remained at 250 beats per minute and continued at that rate for 30 minutes. Cheyne-Stokes respiration began, and finally apnea occurred. Artificial respiration

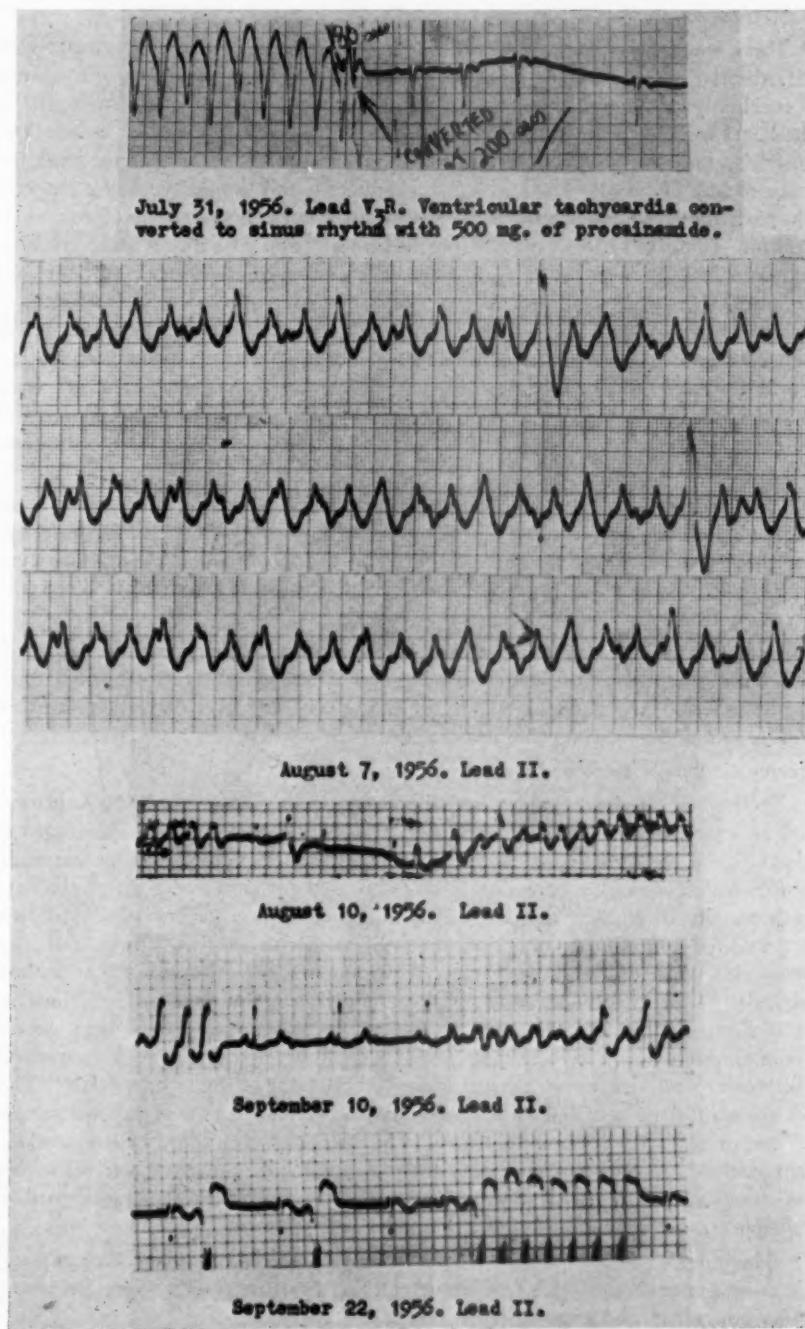


Fig. 3.—Representative samples of ventricular tachycardia occurring at different times.

was used without success and his heart action deteriorated. Cardiac arrest occurred several times and only transient heart beats occurred when his chest was pounded. He expired at 11:30 P.M. on September 22. In the 36 hours preceding death he had received a total of 5 Gm. of quinidine.

Postmortem examination was performed 15½ hours after death. Only the pertinent findings are mentioned.

Gross Examination.—

Heart: There was no significant free fluid in the pericardial cavity. The heart was diffusely and markedly dilated and somewhat enlarged grossly. The epicardial surface was smooth, glistening, and markedly pale, and there was a yellowish discoloration over the right ventricular surface. The heart weighed 535 grams. The myocardium was extremely soft and flabby throughout both ventricles and the interventricular septum, with this condition being most pronounced in the right ventricle. The right ventricle was quite dilated, and the left ventricle showed a moderate, diffuse hypertrophy. There were extensive areas of pale, yellow-tan discoloration throughout the myocardium. Generally, the myocardium appeared pale. In many areas, only occasional patchy, irregular, normal myocardium was seen. The endocardial surface and heart valves were normal. No mural thrombi were present. The coronary ostia were normally situated. The right coronary ostium was half the diameter of the left coronary ostium. There was a markedly preponderant left coronary artery distribution. The right coronary artery was hypoplastic and could be followed only for 3.5 cm. The left coronary artery was large and prominent and widely patent throughout and supplied the entire cardiac circumference. The right ventricular wall showed considerable fatty infiltration. The right atrium was quite dilated. The pulmonary venous return was engorged and congested.

Lungs: The lungs were moderately subcrepitant throughout. The right lung weighed 500 grams, and the left lung, 572 grams. The bronchial and bronchiolar lumina had considerable quantities of thin, watery, serosanguinous fluid. The bronchial mucosal surfaces were diffusely hyperemic. Grossly, the lungs appeared normal except for congestion with serosanguinous fluid exuding on cut section.

Lymph nodes: Prominent pulmonary hilar lymph nodes were present, the largest measuring 1.6 cm. in diameter. Cut section through the larger node revealed multiple small discrete areas of caseation necrosis, the largest being 0.2 cm. in diameter. The liver and spleen were moderately congested. The remainder of the gross examination was normal.

Microscopic Examination.—

Heart: Sections of the heart taken from both ventricles, interventricular septum, and both atria showed an extremely severe, chronic interstitial myocarditis in various stages of activity and resolution (Figs. 4, 5, and 6). In many areas there was extensive disruption and fragmentation of the myocardial fibers. There were numerous focal areas of acute necrosis of the myocardium. Within these areas the fibers presented a swollen, homogeneous, refractile, eosinophilic appearance. There was a marked interstitial, inflammatory cell infiltrate present throughout the sections. In many areas this consisted of plasmacytes, lymphocytes, polymorphonuclear leukocytes, and many eosinophils. There were numerous focal areas of rather marked eosinophilia. There were many areas of fatty infiltration seen throughout the myocardium. There were extensive areas of fibrosis seen throughout many sections. The most striking changes present were throughout the right ventricular wall and within the anteromedial portions of the left ventricle. The coronary arteries and intramural myocardial vessels were entirely normal, and there was no perivascular infiltrates. The myocardial fiber nuclei showed considerable variability in size, shape, and tinctorial characteristics. Occasional muscle fibers showed evidence of acute necrosis with associated loss of cross-striation and acute swelling. There was a rather marked, widespread, interstitial edema. Multiple special stains showed no organisms of any kind.

Lungs: The lungs were normal except for the alveoli, which were filled with extensive smooth amphophilic homogeneous material consistent with edematous fluid. The pulmonary vessels were markedly congested and engorged.

Skeletal muscle: Sections of the diaphragm and pectoral muscles were entirely normal. No granulomatous lesions were found.

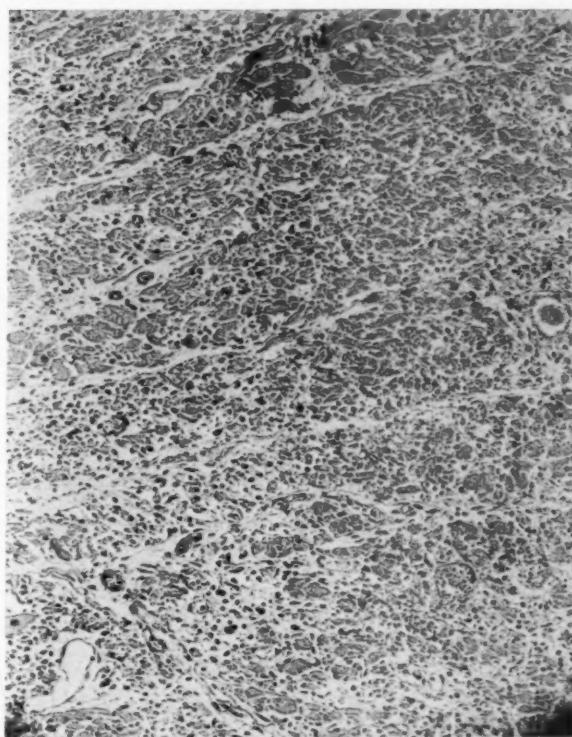


Fig. 4.

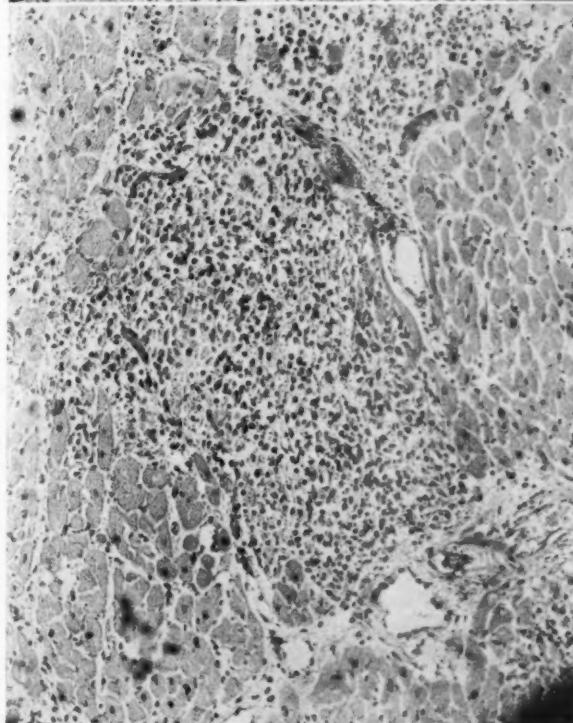


Fig. 5.

Figs. 4 and 5.—Microphotographs of heart showing inflammatory changes and degeneration of heart muscle fibers. Magnification, $\times 430$; reduced $1/5$.

Spleen: An intense and diffuse vascular congestion was seen. There was a diffuse cellular infiltrate of eosinophils scattered in the red pulp. Otherwise, the spleen was normal.

Bone marrow: Bone marrow was normal, and no eosinophilia was seen.

Lymph nodes: Several of the left pulmonary hilar lymph nodes showed multiple, nodular, well-circumscribed areas of caseation necrosis. The necrotic areas had sharply circumscribed, smooth borders of well-organized fibrous tissue. Several lesions had central calcification. Multiple special stains revealed no definitive organisms in the casedated areas.

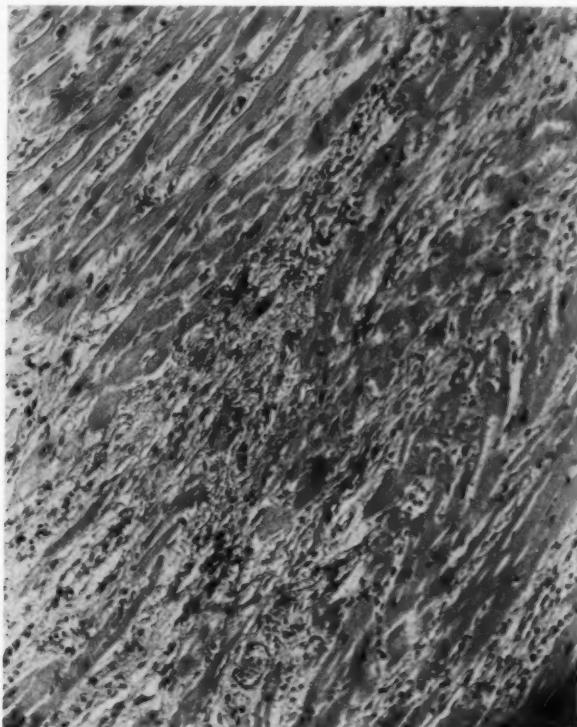


Fig. 6.—Microphotograph of heart showing inflammatory changes and degeneration of heart muscle fibers. Magnification, $\times 430$; reduced $1/5$.

Liver: The liver was normal except for numerous small, well-circumscribed foci of granulomatous inflammation and necrosis scattered throughout the parenchyma. Several were quite large and consisted of abundant, well-circumscribed collections of large, pale epithelial cells with a surrounding cellular infiltrate of mononuclear cells, eosinophils, and occasional polymorphonuclear leukocytes. Centrolobular vascular congestion was also present. Multiple special stains showed no etiologic organism. The kidneys showed only marked vascular congestion and were normal otherwise.

DISCUSSION

Ventricular tachycardia has been reported as occurring in a great many circumstances. Clinically, ventricular tachycardia has been observed in: coronary artery disease,¹⁻⁵ patients with no known heart disease,¹⁻⁷ combined arteriosclerotic hypertensive cardiovascular disease,² hypertensive heart disease,² terminal hypertensive heart disease,¹ rheumatic heart disease,^{2,3,5} rheumatic and hypertensive cardiovascular disease combined,² syphilitic heart disease,²

Wolff-Parkinson-White syndrome,^{3,8} diphtheria,¹ congenital heart disease,³ exertion and/or excitement,^{1,9} idiopathic pericarditis¹⁰; transiently following the stopping of paroxysmal atrial tachycardia by various maneuvers¹¹⁻¹³; and after the administration of various drugs: digitalis^{1-5,14} (especially when digitalis causes the alternate bidirectional type of paroxysmal ventricular tachycardia^{1,4,14-16}), quinidine,^{1-3,17} quinine,¹⁸ norepinephrine and epinephrine,^{19,20} trichloroethylene,^{21,22} cyclopropane,²³ carbon tetrachloride,²² tetraethylammonium (in a patient with pheochromocytoma),²⁴ and Fuadin.²⁵ Experimentally, ventricular tachycardia has been produced by coronary artery occlusion by ligature in dogs,^{26,27} by epinephrine in isolated perfused rabbit hearts pretreated with potassium chloride,²⁸ in association with a rising concentration of potassium in the coronary sinus of dogs with coronary occlusion by ligature,²⁷ by epinephrine in dogs,^{29,30} by procaine in isolated perfused rabbit hearts pretreated with epinephrine,³¹ by application of acetylcholine to, or strong mechanical stimulation of, the dog heart ventricle,³² by trichloroethylene in dogs, by epinephrine or norepinephrine and petroleum ether in the cat,³³ and by rapid electrical stimulation in pigs that have had previous coronary artery ligation.³⁴

Ventricular tachycardia occurring in myocarditis of known etiology is rare. Cossio, Vivoli, and Caul³⁵ presented a case of a 35-year-old sailor who developed paroxysmal ventricular tachycardia 10 days before hospitalization, and died suddenly on the fourteenth hospital day. Postmortem examination of the heart showed lymphocytes and plasma cells surrounding the blood vessels irregularly and in masses. Endarteritis obliterans was seen in the small arteries, and some myocardial fibers were in fragments or were compressed by granulation tissue. The right bundle branch of His was destroyed by granulation tissue. Using Dieterle Roberti's silver impregnation technique, *Treponema pallidum* was observed occasionally around the lymphatic nodules, the septum, and the vasa vasorum of the aorta. But in 1932, Saphir³⁶ reviewed the literature on syphilitic myocarditis, and a critical consideration revealed that morphologically the diagnosis of syphilitic myocarditis could not be made in any of the reviewed cases in the absence of gummas. In Part II of his classic review of myocarditis,³⁷ Saphir stated that Cossio, Vivoli and Caul ". . . described a sclerogummatus type of myocarditis. They included a picture of a spirochete which is not too convincing." After an exhaustive survey, Saphir concluded by stating, ". . . it must be concluded that the entity 'syphilitic myocarditis,' a diffuse syphilitic inflammation with the presence of spirochetes in acquired syphilis, is extremely rare, if it occurs at all." There is a curious case reported by Robinson and Herrmann³⁸ in which a 51-year-old man had paroxysmal ventricular tachycardia because of coronary occlusion. At autopsy, a myocardial infarction was found, with a gummatus lesion in the circumflex branch of the left coronary artery. Also, in this connection, might be mentioned a paper by Froment, Gallavardin and Cahen⁷ in which the authors cite a case of a patient with a positive serology and paroxysmal ventricular tachycardia, in whom the paroxysmal ventricular tachycardia did not recur after treatment of the syphilis.

Schnitzer³⁹ records a case of a 32-year-old white man with pulmonary tuberculosis who developed ventricular tachycardia. He died during an episode

of ventricular tachycardia, and postmortem examination showed miliary and confluent tubercles in the lung and miliary and confluent tubercles in the myocardium, with fibrosis in and around the tubercles. Fibrous granulation tissue with tubercles replaced the outer part of the myocardium of the left ventricle for a distance of 1 cm. There was no tuberculous pericarditis. Johnson and Jason⁴⁰ report a 24-year-old Negro man with sarcoid involving the uvea and lungs, who had a rapid and irregular tachycardia from time to time. An electrocardiogram showed multifocal premature ventricular contractions and paroxysmal ventricular tachycardia. He died on the thirteenth hospital day. Sarcoid was found to involve the heart, lungs, lymph nodes, spleen, liver, and testes. In the heart were early lesions of lymphocytic infiltration and older lesions where muscle fibers were gone and were replaced by epithelioid and giant cells, with a peripheral border of lymphocytes. Culture of the material yielded no acid-fast bacilli. In their classic review of 300 cases of sarcoidosis in 1949, Ricker and Clark⁴¹ mention the case (A.I.P. Accession No. 172709) of a 25-year-old Negro man who was hospitalized in July, 1945, with bilateral decreased vision. In November, 1945, enlarged mediastinal lymph nodes and a pulmonary infiltrate were seen. In January, 1946, epitrochlear and inguinal lymphadenopathy appeared. He developed a pulse of 160, and developed either a "fast fibrillation or a simple ventricular (ectopic) tachycardia." With digitalization his arrhythmia stopped and digitalis was discontinued. His ventricular tachycardia recurred twice more, and he died in February, 1946. Autopsy showed widespread sarcoidosis, with involvement of the heart. In 1951, another case was reported by Adickes, Zimmerman and Cardwell,⁴² that of a 28-year-old Negro man with right upper quadrant abdominal pain, nausea and vomiting, dyspnea, bilaterally enlarged parotid glands and pulmonary hilar lymph nodes, and uveitis. He also had cardiomegaly, a gallop rhythm, and a Grade 3 to 4, harsh, whistling systolic murmur. He developed premature ventricular contractions, and on the twelfth hospital day had paroxysmal ventricular tachycardia. After 3 months of hospitalization he died suddenly. The heart weighed 560 grams, and there were numerous, large areas of scar tissue. A small collection of sarcoid lesions was found in one of the atria. In a clinicopathologic conference in 1957,⁴³ the case of a 33-year-old sailor who had multifocal premature ventricular contractions with short runs of ventricular tachycardia on his electrocardiogram was reported. His arrhythmia was resistant to therapy with procaine amide, and he died suddenly 4 months after onset of the condition. There was extensive granulomatous involvement of the heart by lesions of sarcoid, with extensive fibrosis and some hyalinization of muscle fibers.

Hume⁴⁴ collected six cases of ventricular tachycardia out of 2,400 cases of supraventricular and sinus tachycardia. One of these six cases was that of a 20-year-old man who, during convalescence from diphtheria at the age of 16, began having frequent attacks of palpitation. Over a 3-year period these attacks became less frequent. He was in the British Army for 10 months, and for the last 2 months had more frequent attacks, which were shown to be episodes of paroxysmal ventricular tachycardia and were thought in all probability to be due to diphtheria. Gore,⁴⁵ at the Army Institute of Pathology in 1948, reviewed

221 cases of fatal diphtheria, and of the electrocardiograms recorded in 52 of these, four showed ventricular tachycardia. However, Burkhardt, Eggleston and Smith,⁴⁶ in 1938, over a 2½-year period studied the electrocardiograms in 140 cases of toxic diphtheria and found only 28 cases with electrocardiographic evidence of cardiac damage but none with ventricular tachycardia.

Ventricular tachycardia in rheumatic heart disease is reported by Williams and Ellis² and Ambrust and Levine.³ The former authors list two cases. Details of only one patient are supplied. This was a 34-year-old woman who had cardiomegaly, a loud first sound at the apex of the heart, and a systolic murmur. She was considered to have rheumatic and hypertensive heart disease, with involvement of the mitral valve. The latter authors had nine patients with rheumatic heart disease and paroxysmal ventricular tachycardia. From the data given in these two references it is impossible to know whether rheumatic myocarditis was present in these patients. Saphir and Langendorf,⁴⁷ in 1953, analyzed 22 fatal cases of acute rheumatic heart disease, and of the 12 cases with electrocardiographic records no instance of ventricular tachycardia was found, although other electrocardiographic abnormalities were seen.

Rosenbaum and Alvarez⁴⁸ reviewed the electrocardiographic findings in 130 cases of Chagasic myocarditis. Of these 130 cases, seven showed ventricular tachycardia. One patient had repetitive ventricular tachycardia which he tolerated for 7 years. He had moderate enlargement of the heart but no heart failure. Laranja and associates⁴⁹ surveyed 1,340 chronic cases of Chagas' disease, of which 683 had evidence of myocardial damage. In this latter group there were 14 cases of ventricular tachycardia, 12 of which were fatal cases.

Gore and Saphir,⁵⁰ at the Army Institute of Pathology in 1947, collected 35 cases of fatal myocarditis associated with acute nasopharyngitis (23 cases) and acute tonsillitis (12 cases). Case No. 6 (A.I.P. Accession No. 140417) was a 31-year-old white man who was hospitalized for acute tonsillitis and treated with sulfadiazine. The process had largely resolved by the ninth day, when he complained of sudden pain. His heart sounds were poor, the rhythm was irregular, and the blood pressure was 85/70 mm. Hg. This persisted through the next day. Pulmonary edema occurred, and his electrocardiogram showed ventricular tachycardia. Anuria developed and he died. At postmortem examination he was found to have a diffuse myocarditis. There was cardiac dilatation and gross alterations of the myocardium. There was a moderate amount of muscle necrosis. Whether these cases of myocarditis are fortuitously coincident with the upper respiratory infections or are causally related is difficult to establish, but their close association cannot be easily discounted.

Finally, Javett and associates⁵¹ described 10 cases of myocarditis in infants, six of which cases had a fatal outcome. Group B Coxsackie virus was discovered in four infants, one of whom developed ventricular tachycardia and expired 1 hour after admission to the hospital.

Ventricular tachycardia occurring in myocarditis of unknown etiology rarely has been encountered. In 1926, Major and Wahl⁵² cited the case of a 25-year-old man who had an attack of tachycardia at the age of 12 and again at the age of 19, and who also had infected tonsils for several years and badly

infected teeth for 18 months. He developed paroxysmal ventricular tachycardia with a rate of 200 to 240 per minute and was admitted to the hospital. Three hours after he had received two thirds of a grain of Pantopon orally and 0.025 mg. of ouabain by hypodermic injection, his pulse became 100. He was discharged from the hospital the next day. Four months later his tachycardia recurred, and again after 0.025 mg. of ouabain was instituted his tachycardia ceased. Five hours later another attack occurred and he died in 3 minutes. At the time of death there was a marked quivering of the precordium. Post-mortem examination showed foci of polymorphonuclears, with collections of mononuclear cells and eosinophils in the right and left atria, left ventricle, and interventricular septum, including the bundle of His. A large amount of degeneration of muscle fibers was seen in all sections.

Rubell and Strauss,⁵³ in 1936, reported a child who had attacks of paroxysmal ventricular tachycardia simulating epileptic seizures from the age of 3 years until her death during one such bout at the age of 8 years. On occasions, severe apprehension or fright precipitated the attacks. At autopsy there was marked fibrosis of the right atrium, including the sinus node, portions of the interventricular septum, including the A-V node and bundle of His, and papillary muscles of the left ventricle. Occasionally, inflammatory cells, usually lymphocytes, were seen within the fibrotic areas. No etiology was found to account for this myocarditis.

In 1954, de la Chapelle and Kossmann,⁵⁴ in a review of myocarditis, mention ventricular tachycardia only to say that, "Ventricular tachycardia has been encountered principally in terminal instances of diphtheritic myocarditis," but they give no documentation for this statement. The authors also mention that, ". . . we have observed an example of ventricular and bidirectional ventricular tachycardia in the course of acute focal myocarditis of unknown cause." The captions under the figures relating to the case indicate that the patient was a 42-year-old Puerto Rican woman with acute focal interstitial myocarditis who also had some hemorrhage into the epicardial fat. The heart weighed 420 grams. Her electrocardiogram showed low voltage of the QRS complex with inverted T waves in Leads V₂ and V₄. Shortly after onset of the shock-like state 2 days before death the electrocardiogram showed a bidirectional ventricular tachycardia. Duration of the ventricular tachycardia is not stated. Whether or not the patient was receiving digitalis at the time is not stated.

A case presented at a clinicopathologic conference at the Massachusetts General Hospital⁵⁵ was that of a 24-year-old man who had suffered with grand mal seizures for 2½ years, and for which he had received Dilantin. For 5 months before hospitalization he had episodes of palpitation, nausea and vomiting, and loss of consciousness. An electrocardiogram during one of these showed ventricular tachycardia that spontaneously reverted to normal. Later, he was hospitalized with the symptom of pressure in his chest, and was found to have ventricular tachycardia with a rate of 240. He was given procaine amide, and normal sinus rhythm ensued. Frequent episodes of ventricular tachycardia took place, but he had no cardiomegaly. On therapy with procaine amide he had no further episodes of tachycardia, and was discharged on the fifteenth

hospital day. Four weeks later he was found dead in bed. Autopsy showed diffuse fibrosis of the myocardium, which was thought probably to be secondary to myocarditis.

Levy and Von Glahn⁵⁶ described 10 cases of an entity that they labeled as cardiac hypertrophy of unknown cause. Their Case No. 8 was that of a 66-year-old white woman who died during a paroxysm of ventricular tachycardia 2 months after admission to hospital. At the age of 7 years this patient had had diphtheria, and had had "generalized dropsy" requiring bed rest for 1 year. Pneumonia occurred at ages 20 and 21, and tuberculosis at age 23; the latter was cured in 1 year. She remained well until age 52, when she was told that she had a large heart. Six months prior to admission to the hospital her heart rate became greater than 200, and she had dyspnea. Pulmonary congestion, dyspnea, and edema persisted thereafter. At the time of admission she had an enlarged liver, the point of maximum impulse of the heart was at the anterior axillary line, and her pulse was 42. She had episodes of complete and partial A-V block. Paroxysms of ventricular tachycardia occurred which responded to quinidine therapy. A left facial palsy and right hemiplegia occurred 2 days prior to death. Terminally, her temperature rose to 104.4° F. She died during a paroxysm of ventricular tachycardia. Autopsy showed an enlarged heart weighing 440 grams. The myocardium of the atria was hypertrophied and diffusely scarred. The right ventricle showed areas of recent necrosis frequently involving branches of the conduction system. There was myocardial necrosis in the interventricular septum. There were scars of loose connective tissue, with phagocytes in the scar which were filled with a pale yellow granular pigment. Similar changes were found in the left ventricle and papillary muscles. Aggregates of small mononuclear cells were seen about or near some of the arterioles.

One further case may be cited, which is however of a less well-defined nature than those mentioned above. In 1938, Amberg and Willius⁵⁷ observed a 15-month-old girl who had diarrhea for 3 weeks; when the diarrhea subsided, she developed a cough, dyspnea, and moist râles in the lungs. Cardiomegaly and tachycardia occurred, and on the fourth hospital day paroxysmal ventricular tachycardia was recorded electrocardiographically. The patient died on the eleventh hospital day. The heart weighed 130 grams (42 grams being normal for this age), and the myocardium showed moderate degrees of fatty degeneration. The authors were unable to establish a cause of the cardiac disease. No detailed description of the microscopic appearance of the heart was given.

Thus, we may conclude that myocarditis of known and unknown etiology can cause ventricular tachycardia and should be added to the long list of conditions already associated with ventricular tachycardia. Although idiopathic myocarditis usually presents as unexplained cardiac failure⁵⁸⁻⁶⁰ or sudden death,^{58, 61-68} it may present rarely as ventricular tachycardia. One may speculate that cases of ventricular tachycardia with no apparent cardiac disease, such as reported by Ambrust and Levine,³ may in some instances represent some type of myocarditis which is nonprogressive and relatively well tolerated. Chagasic myocarditis is a myocarditis which is known to behave in this fashion, and Rosenbaum

and Alvarez⁴⁸ point out that in practically every case of chagasic myocarditis the electrocardiographic tracing becomes abnormal before the heart enlarges and before clinical symptoms and signs are noticeable.

The mechanism of the development of the ventricular tachycardia in our case was most likely the direct irritation of normal or minimally damaged muscle fibers by the severe inflammatory process taking place in the myocardium, with multiple foci initiating the ventricular contractions. When many such foci in rapid sequence were operating, the bizarre pattern that our patient had was seen. When the ventricular foci acted relatively less frequently, multifocal premature ventricular contractions were seen interpolated between normal electrocardiographic complexes. As the foci began occurring closer together, the normal complexes became scarcer, short runs of ventricular tachycardia occurred, and finally, persistent ventricular tachycardia developed. Possibly, degenerating myocardial muscle fibers contribute irritable foci to the arrhythmia. That this may be so is supported by the study of Zatuchni, Aegeleter, Molthan and Shuman⁶⁹ of 292 cases of progressive muscular dystrophy. Of 136 cases in which cardiac data were available, 94 showed some abnormality of the cardiovascular system. Seven patients had tachycardia asleep and awake, and the heart accelerated with minimal stimuli. Two patients had extrasystoles and ventricular tachycardia. These cases, reviewed by Zatuchni and his colleagues, represent primary, noninflammatory muscle disease of the heart. Thus, inflammatory processes or irritation of the conduction system of the heart cannot be invoked as mechanisms for the arrhythmia. The direct mechanism may be mediated by the local destruction of tissue by the inflammatory process, which releases potassium locally, and the potassium then acts as the primary excitant. This idea is supported by the work of Cherbakoff, Toyama and Hamilton,²⁷ who found that when the left coronary artery in dogs was ligated, there was a rise in the concentration of potassium in the coronary sinus blood, accompanied by a rapid series of extrasystoles that ended in ventricular fibrillation 5 minutes after ligation in five of nine animals. In three animals, as the level of potassium rose, short bursts of extrasystoles and/or ventricular tachycardia occurred, and as the level of potassium decreased, the extrasystoles were suppressed. A second rise in the level of potassium again took place, extrasystoles and/or ventricular tachycardia occurred, and ventricular fibrillation finally took place. Ventricular fibrillation usually occurred after a paroxysm of ventricular tachycardia. One dog had no rise in the level of potassium after coronary artery ligation. This dog did not develop extrasystoles or ventricular tachycardia. Finally, direct irritation of the conduction system of the heart by the active inflammatory process and/or the resultant scar tissue should be mentioned. This might be more likely to lead to varying degrees of atrioventricular block, even though one cannot exclude the possibility that this may be a factor in the production of premature ventricular contractions and ventricular tachycardia. But one would expect that unifocal premature ventricular contractions would predominate. Lesions involving the conduction system of the heart have been found in postmortem examinations of the cases cited above,^{35,52,53,56} and, although not mentioned in the other cases, one cannot exclude the presence of lesions irritating

the conduction system in those cases. All of the mechanisms may participate to varying degrees in any given case. However, if potassium is involved, it would be dangerous indeed to use potassium solutions as a therapeutic measure except in the case of digitalis-induced ventricular tachycardia.

Another electrocardiographic change, consisting of inverted T waves in the right precordial leads, was seen in our patient (Fig. 2). These changes have been described by others in many varieties of myocarditis.^{46-49,54,58,59,64,70-74} It would seem that the T-wave inversion in our patient was a direct reflection of his myocarditis. A so-called post-tachycardia syndrome has been described as appearing in some cases of paroxysmal ventricular tachycardia after the cessation of the ventricular tachycardia. This usually consists of T-wave inversion persisting for varying lengths of time (6 to 60 days), S-T segment depression, and prolongation of the Q-T interval.^{7,75-78} In none of the patients in whom this has been described has pathologic examination of the heart been performed. Since we do not know what the post-tachycardia syndrome represents, it does not seem reasonable to invoke it to explain the T-wave inversion in this patient's electrocardiogram. The more logical explanation is that probably it was due to his myocarditis, particularly in view of the pathologic findings of acute myocarditis and fibrosis, especially in the anteromedial wall of the left ventricle. It may be that the post-tachycardia syndrome itself represents a transient myocarditis which was responsible for the paroxysmal ventricular tachycardia in the first place.

One of the striking changes noted pathologically was a diffuse eosinophilia in many parts of the heart. This probably represents the eosinophilia often seen in the healing phase of inflammatory lesions. Eosinophilia has been noted before in myocarditis and in the heart in a variety of other conditions. Eosinophilia in the myocardium has been described in diphtheritic myocarditis,⁷⁹ so-called eosinophilic leukemia,⁸⁰ larva migrans due to *Toxocara* larva,⁸¹ bronchial asthma,⁸² allergic granulomatosis,⁸³ and rarely in acute rheumatic carditis,⁸⁴ trichinosis,^{85,86} teniasis,⁸⁷ toxoplasmosis,⁸⁸ as well as in myocarditis of unknown etiology.^{68,90-97} Thus, such eosinophilia is of a nonspecific nature, and the exact significance of eosinophilia in the heart cannot be stated.

Therapy in this patient was extremely difficult. He responded at times to procaine amide and quinidine gluconate given intravenously. But these provided only temporary respites, and multifocal premature ventricular contractions continued. Finally, during a paroxysm of ventricular tachycardia, heart action deteriorated, and despite all measures the patient expired. Lacking specific means to arrest the inflammatory process in this patient's myocardium, only symptomatic treatment could be used. The use of quinidine in the treatment of ventricular tachycardia is solidly grounded in the past experiences of others.^{3,5,14} Binder and Rosove¹⁷ collected 20 cases from the literature in which quinidine was implicated in the production of ventricular tachycardia and/or ventricular fibrillation, and added two cases of their own. They noted that doses as small as 1.2 Gm. in one case and 0.4 Gm. in two other cases resulted in ventricular tachycardia. On the other hand, Levine⁹⁸ gave 7.5 Gm. of quinidine in one day, and Reich⁹⁹ used 12.3 Gm. in 2½ days and cites other cases in which large doses

of quinidine have been used. Williams and Ellis² noted that daily doses as high as 5.82 Gm. have been given repeatedly without untoward result. Strong and Munroe¹⁰⁰ successfully treated a 41-year-old man with 2.59 Gm. of quinidine sulfate, intravenously, after 23 days of continuous ventricular tachycardia. Morris and Franklin¹⁰ gave 3.2 Gm. of quinidine gluconate intravenously in 4 hours in a young man with ventricular tachycardia, without effect, but on the third day normal sinus rhythm occurred after the use of 1.5 Gm. each of quinidine gluconate and procaine amide, intravenously. Dubbs and Parmet⁷⁸ converted a ventricular tachycardia of 21 days' duration to regular sinus rhythm with 1.0 Gm. of quinidine sulfate given intravenously. It would seem then that ventricular tachycardia from quinidine is quite infrequent and is not too well correlated with the dose. In all probability it had no effect on our patient in the terminal phase of his illness, neither aggravating or alleviating his ventricular tachycardia.

We cannot say what the underlying etiology was in this case. But certain causes can be considered. A great many causes of myocarditis are known and have been listed by Gore and Saphir¹⁰¹ and Baggeneoss and Stryker.¹⁰² But none of those causes, associated with known disease, apply to this case. It is tempting to consider a virus as a possible cause. Unfortunately, the nature of the patient's disease was not anticipated, so that suitable specimens were not kept for viral studies. Saphir, Amromin and Yokoo¹⁰³ listed many of the viral diseases in which myocarditis occurs, such as poliomyelitis, measles, mumps, viral pneumonia, encephalitis, and infectious mononucleosis, and reported four cases of myocarditis occurring in infectious hepatitis. Kibrick and Benirschke¹⁰⁴ isolated a Group B, Type 3 Coxsackie virus from the renal tissue of an infant dying of encephalomyocarditis. The myocardium was infiltrated with polymorphonuclear leukocytes, macrophages, and occasional lymphocytes, and there were numerous eosinophils. They reviewed similar reported cases and summarized the findings. These cases of viral myocarditis had microscopic pictures of acute interstitial myocarditis. If the technique for viral studies had not been developed, these cases would have fit the concept of myocarditis of unknown etiology (which has been classified as so-called "isolated myocarditis" by numerous authors). Thus, a viral etiology remains a very real possibility. A "musculotropic virus" might be postulated. The Coxsackie virus is one such type. In such a case other muscle besides cardiac muscle might be expected to be involved. Indeed, another patient with myocarditis at Walter Reed Army Hospital had smooth muscle and mucosa of the gastrointestinal tract involved, with a resulting malabsorption syndrome.¹⁰⁵

On the other hand, cases of myocarditis with involvement of the skeletal muscles have been described and have been categorized as "thyrotoxic myopathy." Terplan and associates¹⁰⁶ had a patient with thyrotoxicosis with far-advanced exophthalmos and a myositis characterized by extensive necrosis of muscle fibers involving most of the skeletal musculature. The heart and extraocular muscles were the most severely involved. Marked eosinophilia of the tissues was found. Wright¹⁰⁶ reported a similar case of a patient with so-called

"malignant exophthalmos" associated with a fatal myocarditis, and at least one similar case is contained in the files of the Armed Forces Institute of Pathology.¹⁰⁷

Not to be overlooked is the concept of myocarditis due to hypersensitivity. Neustadt¹⁰⁹ reviewed this possibility in the discussion of a case report. A young woman developed acute serum sickness after being given tetanus antitoxin, and 3 days later she was admitted to the hospital. On the second hospital day her electrocardiogram showed inverted T waves in Leads II, III, V₃, and aV_F. On the fourth hospital day there was very slight T-wave inversion in Lead II, with the T waves upright elsewhere. These changes were thought to have been due possibly to an allergic myocarditis. Neustadt cited the experimental evidence in favor of the concept of allergic myocarditis and cited cases of myocarditis associated with drug sensitivity.

It would seem likely, however, that multiple causes will be uncovered. Now that procedures are available to investigate the possibility of the viral etiology of myocarditis, a better understanding of myocarditis as a clinical entity should result.

SUMMARY

The case of a 19-year-old patient with multifocal premature ventricular contractions and frequent bouts of ventricular tachycardia culminating fatally, with pathologic findings of myocarditis, is presented. This patient had little other clinical evidence of cardiac disease. Other causes of ventricular tachycardia are discussed and other cases of myocarditis of known and unknown etiology with ventricular tachycardia are reviewed. It is pointed out that ventricular tachycardia can be the predominant manifestation of myocarditis, and the possibility is suggested that cases of ventricular tachycardia with no apparent heart disease may represent less serious forms of myocarditis. Some possibilities as to the mechanism of ventricular tachycardia are mentioned. Possible causes for the myocarditis in this case are discussed briefly.

REFERENCES

1. Lundy, C. J., and McLellan, L. L.: Paroxysmal Ventricular Tachycardia: An Etiological Study With Special Reference to the Type, *Ann. Int. Med.* **7**:812, 1934.
2. Williams, C., and Ellis, L. B.: Ventricular Tachycardia. An Analysis of 36 Cases, *Arch. Int. Med.* **71**:137, 1943.
3. Ambrust, C. A., and Levine, S. A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases, *Circulation* **1**:28, 1950.
4. Cooke, W. T., and White, P. D.: Paroxysmal Ventricular Tachycardia, *Brit. Heart J.* **5**:33, 1943.
5. Herrmann, G. R., and Hejtmancik, M. R.: A Clinical and Electrocardiographic Study of Paroxysmal Ventricular Tachycardia and Its Management, *Ann. Int. Med.* **28**:989, 1948.
6. Ring, A., and Blankfein, J.: Paroxysmal Ventricular Tachycardia in an Apparently Normal Heart, *Ann. Int. Med.* **42**:680, 1955.
7. Froment, R., Gallavardin, L., and Cahen, P.: Paroxysmal Ventricular Tachycardia. A Clinical Classification, *Brit. Heart J.* **15**:172, 1953.
8. Dunn, J. J., Sarrell, W., and Franklin, R. B.: The Wolff-Parkinson-White Syndrome Associated With Paroxysmal Ventricular Tachycardia, *Am. HEART J.* **47**:462, 1954.
9. Peters, M., and Penner, S. L.: Orthostatic Paroxysmal Ventricular Tachycardia, *Am. HEART J.* **32**:645, 1946.

10. Morris, G. M., and Franklin, R. B.: Ventricular Tachycardia Due to Idiopathic Pericarditis Controlled by Simultaneous Intravenous Procaine Amide and Quinidine, *AM. HEART J.* **47**:919, 1954.
11. Hollander, W., and Entwistle, G.: Transient Ventricular Tachycardia Following the Val-salva Maneuver in a Patient With Paroxysmal Atrial Tachycardia, *AM. HEART J.* **52**:799, 1956.
12. Landman, M. E., and Ehrenfeld, I.: Ventricular Fibrillation Following Eyeball Pressure in a Case of Paroxysmal Atrial Tachycardia, *AM. HEART J.* **43**:791, 1952.
13. Meredith, H. C., Jr., and Beckwith, J. R.: Development of Ventricular Tachycardia Following Carotid Sinus Stimulation in Paroxysmal Supraventricular Tachycardia, *AM. J. HEART* **39**:604, 1957.
14. Freundlich, J.: Paroxysmal Ventricular Tachycardia, *AM. HEART J.* **31**:557, 1946.
15. Zimdhahl, W. T., and Townsend, C. E.: Bidirectional Ventricular Tachycardia Due to Digitalis Poisoning. Response to Potassium Therapy and Evaluation of Arrhythmia Mechanism, *AM. HEART J.* **47**:304, 1954.
16. Braun, L., and Wosika, P. H.: Bidirectional Paroxysmal Tachycardia: Toxicity of Different Cardiac Glycosides, *AM. HEART J.* **29**:261, 1945.
17. Binder, M. J., and Rosove, L.: Paroxysmal Ventricular Tachycardia and Fibrillation Due to Quinidine, *Am. J. Med.* **12**:491, 1952.
18. Diamondstone, A. H., Braverman, B. L., and Baker, L. A.: Ventricular Tachycardia and Bilateral Amaurosis Produced by Quinine Poisoning, *Arch. Int. Med.* **80**:763, 1947.
19. Goodman, L. S., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, Ed. 2, New York, 1955, The Macmillan Co., pp. 487 and 501.
20. Nathanson, M. H., and Miller, H.: The Action of Norepinephrine, Epinephrine, and Isopropylnorepinephrine on the Rhythmic Function of the Heart, *Circulation* **6**:238, 1952.
21. Waters, R. M., Orth, O. S., and Gillespie, N. A.: Trichlorethylene Anesthesia and Cardiac Rhythm, *Anesthesiology* **4**:1, 1943.
22. Geiger, A. J.: Cardiac Dysrhythmia and Syncope, *J.A.M.A.* **123**:141, 1943.
23. Nickerson, M., and Brown, H. O.: Protection by Dibenamine Against "Spontaneous" Arrhythmias Occurring During Cyclopropane Anesthesia, *Anesthesiology* **12**:216, 1951.
24. Gould, J., and Mundal, A. L.: Multifocal Ventricular Tachycardia Induced by Etamon in a Case of Pheochromocytoma, *AM. HEART J.* **42**:460, 1951.
25. Schick, R., Ritterband, A. B., and Lieberman, A. H.: Fuadin Therapy of Schistosomiasis Associated With Ventricular Tachycardia and Death. A Case Report, *Ann. Int. Med.* **46**:392, 1957.
26. Smith, F. H., McEachern, C. G., and Hall, G. E.: The Effect of the Intravenous Administration of Quinidine Sulfate on the Development of Ventricular Fibrillation Following Sudden Occlusion of the Circumflex Branch of the Left Coronary Artery, *AM. HEART J.* **20**:620, 1940.
27. Cherbakoff, A., Toyama, S., and Hamilton, W. F.: Relation Between Coronary Sinus Plasma Potassium and Cardiac Arrhythmia, *Circulation Res.* **5**:517, 1957.
28. Grumbach, L.: The Initiation of Ventricular Tachycardia and Fibrillation in Isolated Hearts by Potassium Chloride, *Circulation Res.* **4**:293, 1956.
29. Wilburne, M., Surtshin, A., Rodbard, S., and Katz, L. N.: Inhibition of Paroxysmal Ventricular Tachycardia by Atropine, *AM. HEART J.* **34**:860, 1947.
30. Lenel, R., Vanloo, A., Rodbard, S., and Katz, L. N.: Factors Involved in the Production of Paroxysmal Ventricular Tachycardia Induced by Epinephrine, *Am. J. Physiol.* **153**:553, 1948.
31. Grumbach, L.: The Initiation of Ventricular Tachycardia and Fibrillation by Procaine in the Isolated Perfused Rabbit Heart, *Circulation Res.* **4**:112, 1956.
32. Scherf, D., and Chick, F. B.: Abnormal Cardiac Rhythms Caused by Acetylcholine, *Circulation* **3**:764, 1951.
33. Garb, S., and Chenoweth, M. B.: Studies on Hydrocarbon-Epinephrine Induced Ventricular Fibrillation, *J. Pharmacol. & Exper. Therap.* **94**:12, 1948.
34. Zoll, P. M., Paul, M. H., Linenthal, A. J., Norman, L. R., and Gibson, W.: The Effects of External Electric Currents on the Heart. Control of Cardiac Rhythm and Induction and Termination of Cardiac Arrhythmias, *Circulation* **14**:745, 1956.
35. Cossio, P., Vivoli, D., and Caul, H.: Syphilis of the Interventricular Septum and Ventricular Tachycardia, *Am. J. M. Sc.* **194**:369, 1937.
36. Saphir, O.: Syphilitic Myocarditis, *Arch. Path.* **13**:266 and 436, 1932.
37. Saphir, O.: Myocarditis. A General Review With an Analysis of 240 Cases, Part II, *Arch. Path.* **33**:88, 1942.
38. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Ventricular Tachycardia and Its Relation to Coronary Occlusion, *Heart* **8**:59, 1920-1921.
39. Schnitzer, R.: Myocardial Tuberculosis With Paroxysmal Ventricular Tachycardia, *Brit. Heart J.* **9**:213, 1947.

40. Johnson, J. B., and Jason, R. S.: Sarcoidosis of the Heart. Report of a Case and Review of the Literature, *AM. HEART J.* **27**:246, 1944.
41. Ricker, W., and Clark, M.: Sarcoidosis, A Clinicopathologic Review of 300 Cases, Including 22 Autopsies, *Am. J. Clin. Path.* **19**:725, 1949.
42. Adickes, G. C., Zimmerman, S. L., and Cardwell, E. S., Jr.: Sarcoidosis With Fatal Cardiac Involvement, *Ann. Int. Med.* **35**:898, 1951.
43. Clinicopathological Conference—Cardiac Arrhythmia, U. S. Armed Forces *M. J.* **8**:855, 1957.
44. Hume, W. E.: Observations in 6 Cases of Paroxysmal Ventricular Tachycardia, *Quart. J. Med.* **11**:131, 1918.
45. Gore, I.: Myocardial Changes in Fatal Diphtheria. A Summary of Observations in 221 Cases, *Am. J. M. Sc.* **215**:257, 1948.
46. Burkhardt, E. A., Eggleston, C., and Smith, L. W.: Electrocardiographic Changes and Peripheral Nerve Palsies in Toxic Diphtheria, *Am. J. M. Sc.* **195**:301, 1938.
47. Saphir, O., and Langendorf, R.: Nonspecific Myocarditis in Acute Rheumatic Fever, *AM. HEART J.* **46**:432, 1953.
48. Rosenbaum, M. B., and Alvarez, A. J.: The Electrocardiogram in Chronic Chagasic Myocarditis, *AM. HEART J.* **50**:492, 1955.
49. Laranja, F. S., Dias, E., Nobrega, G., and Miranda, A.: Chagas' Disease. A Clinical, Epidemiologic and Pathologic Study, *Circulation* **14**:1035, 1956.
50. Gore, I., and Saphir, O.: Myocarditis Associated With Acute Nasopharyngitis and Acute Tonsillitis, *AM. HEART J.* **34**:831, 1947.
51. Javett, S. N., Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. I., Gear, J., Measroch, V., and Kirsch, Z.: Myocarditis in the Newborn Infant. A Study of an Outbreak Associated With a Coxsackie Group B Virus Infection in a Maternity Home in Johannesburg, *J. Pediat.* **48**:1, 1956.
52. Major, R. H., and Wahl, H. R.: Paroxysmal Tachycardia Associated With Focal Myocarditis, *J.A.M.A.* **86**:1125, 1926.
53. Rubell, I., and Strauss, H.: Fatal Paroxysmal Ventricular Tachycardia in a Young Child, *Am. J. Dis. Child.* **51**:633, 1936.
54. de la Chapelle, C. E., and Kossmann, C. E.: Myocarditis, *Circulation* **10**:747, 1954.
55. Case Records of the Massachusetts General Hospital. Case 42182, *New England J. Med.* **254**:859, 1956.
56. Levy, R. L., and Von Glahn, W. C.: Cardiac Hypertrophy of Unknown Cause. A Study of Clinical and Pathologic Features in Ten Adults, *AM. HEART J.* **28**:714, 1944.
57. Amberg, S., and Willius, F. A.: Cardiac Clinics. Clinic on Ventricular Tachycardia Occurring in an Infant; Cardiac Hypertrophy of Unknown Origin; Course: Post-Mortem Findings: Comment: Discussion, *Proc. Staff Meet. Mayo Clin.* **13**:470, 1938.
58. Lustok, M. J., Chase, J., and Lubitz, J. M.: Myocarditis: A Clinical and Pathologic Study of 45 Cases, *Dis. Chest* **28**:243, 1955.
59. Williams, H.: Idiopathic Myocarditis in Infancy and Childhood, *M. J. Australia* **1**:76, 1953.
60. Bailey, F. R., and Andersen, D. H.: Acute Interstitial Myocarditis, *AM. HEART J.* **6**:338, 1931.
61. Helwig, F. C., and Wilhelmy, E. W.: Sudden and Unexpected Death From Acute Interstitial Myocarditis: A Report of 3 Cases, *Ann. Int. Med.* **13**:107, 1939.
62. Moritz, A. R., and Zamcheck, N.: Sudden and Unexpected Deaths of Young Soldiers, *Arch. Path.* **42**:459, 1946.
63. Gore, I., and Saphir, O.: Myocarditis Associated With Acute and Subacute Glomerulonephritis, *AM. HEART J.* **36**:390, 1948.
64. Dilling, N. V.: Giant Cell Myocarditis, *J. Path. & Bact.* **71**:295, 1956.
65. Karni, H.: Sudden Death Due to Myocarditis. A Clinical and Pathological Study, *Acta med. scandinav.* **149**:243, 1954.
66. Gormsen, H.: Sudden Unexpected Death Due to Myocarditis, *Acta path. et microbiol. scandinav.* **105**:30, 1955. Cited by Faber and Fischer.⁵⁹
67. Boemke, F.: Der Plotzlich Tod aus natürlicher Ursache bei Soldaten Wahrend des vergangenen Krieges, Frankfurt. *Ztschr. Path.* **59**:104, 1947.
68. Saphir, O.: Isolated Myocarditis, *AM. HEART J.* **24**:167, 1942.
69. Zatuchni, J., Aegeerter, E. E., Molthan, L., and Shuman, C. R.: The Heart in Progressive Muscular Dystrophy, *Circulation* **3**:846, 1951.
70. Saphir, O., Katz, L. N., and Gore, I.: The Myocardium in Subacute Bacterial Endocarditis, *Circulation* **1**:1155, 1950.
71. Conlin, G. J., Jr., and Mantz, F. A., Jr.: Isolated Myocarditis in Infants, *J. Pediat.* **42**:414, 1953.
72. Gouley, B. A., McMillan, T. M., and Bellet, S.: Idiopathic Myocardial Degeneration Associated With Pregnancy and Especially the Puerperium, *Am. J. M. Sc.* **194**:185, 1937.
73. Freeman, Z.: A Case of Fiedler's Myocarditis Simulating Pericardial Effusion, *M. J. Australia* **42**:273, 1955.

74. Gydell, K., Biorck, G., and Winblad, S.: Acute Fatal Myocarditis. Clinico-Pathological Analysis of 15 Cases of Fatal Myocarditis and Some Diagnostic and Therapeutic Considerations, *Acta med. scandinav.* **151**:1, 1955.
75. Zimmerman, S. L.: Transient T-Wave Inversion Following Paroxysmal Tachycardia, *J. Lab. & Clin. Med.* **29**:598, 1944.
76. Ward, L. S.: Abnormal Electrocardiogram Following Recovery From Paroxysmal Tachycardia, *AM. HEART J.* **31**:645, 1946.
77. Smith, L. B.: Paroxysmal Ventricular Tachycardia Followed by Electrocardiographic Syndrome, *AM. HEART J.* **32**:257, 1946.
78. Dubbs, A. W., and Parmet, D. H.: Ventricular Tachycardia Stopped on the 21st Day by Giving Quinidine Sulfate Intravenously, *AM. HEART J.* **24**:272, 1942.
79. Nuzum, F.: Eosinophilous Myocarditis in Diphtheria, *J.A.M.A.* **73**:1925, 1919.
80. Fadell, E. J., Crone, R. I., Leonard, M. E., and Altamirano, M.D.: Eosinophilic Leukemia, *A.M.A. Arch. Int. Med.* **99**:819, 1957.
81. Brill, R., Churg, J., and Beaver, P. C.: Allergic Granulomatosis Associated With Visceral Larva Migrans, *Am. J. Clin. Path.* **23**:1208, 1954.
82. Chafee, F. H., Ross, J. R., and Gunn, E. M.: Eosinophilia in Fatal Asthma; Studies of Bone Marrow and Myocardium, *Ann. Int. Med.* **17**:45, 1942.
83. Walter Reed Army Hospital Autopsies, Vol. 87, Case No. 5608, 1952.
84. Watjen, J.: Ein besonderer Fall rheumatischer Myokarditis. *Verhandl. Deutsch. path. Gesellsch.* **18**:223, 1921.
85. Gould, S. E.: Trichinosis, Springfield, Ill., 1945, Charles C Thomas, pp. 117-124.
86. Spink, W. W.: Cardiovascular Complications of Trichinosis, *Arch. Int. Med.* **56**:238, 1935.
87. Freund: *Berl. klin. Wchnschr.* **49**:50, 1898: Cited by Nuzum.⁷⁹
88. Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, *Arch. Path.* **30**:374, 1940.
89. Faber, V., and Fischer, S.: Acute Idiopathic Myocarditis, *Acta med. scandinav.* **154**:135, 1956.
90. Saphir, O.: Myocarditis. A General Review With an Analysis of 240 Cases, Part I, *Arch. Path.* **32**:1000, 1941.
91. Boikan, W. S.: Myocarditis Pernicosa. *Virchows Arch. path. Anat.* **282**:46, 1931.
92. Sikl, H.: Eosinophile Myokarditis als idiosynkrasischallergische Erkrankung, *Frankfurt. Ztschr. Path.* **49**:283, 1936.
93. Marcuse, P. M.: Nonspecific Myocarditis. Analysis of 36 Cases, *Arch. Path.* **43**:602, 1947.
94. Coulter, W. W., and Marcuse, P.: Acute Isolated Myocarditis, *Am. J. Clin. Path.* **14**:399, 1944.
95. Simon, M. A., and Wolpaw, S.: Acute, Subacute and Chronic Isolated Myocarditis, *Arch. Int. Med.* **56**:1136, 1935.
96. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following the Clinical and Experimental Use of Sulfonamide Drugs, *Am. J. Path.* **18**:109, 1942.
97. Tesluk, H.: Giant Cell Versus Granulomatous Myocarditis, *Am. J. Clin. Path.* **26**:1326, 1956.
98. Levine, S. A.: Clinical Heart Disease, Ed. 3, Philadelphia, 1946, W. B. Saunders Co., pp. 201-203.
99. Reich, N. E.: Successful Use of a Massive Dose of Quinidine in a Case of Intractable Ventricular Tachycardia, *AM. HEART J.* **28**:256, 1944.
100. Strong, G. F., and Munroe, D. S.: Paroxysmal Ventricular Tachycardia and Report of an Unusual Case, *AM. HEART J.* **19**:486, 1940.
101. Gore, I., and Saphir, O.: Myocarditis. A Classification of 1,402 Cases, *AM. HEART J.* **34**:827, 1947.
102. Baggenstoss, A. H.: Rheumatic Myocarditis, pp. 647-656; Non-Rheumatic Myocarditis, pp. 784-835; and Stryker, W. A.: Parasitic Disease of the Heart, pp. 836-851. In Gould, S. E.: Pathology of the Heart, Springfield, Ill., 1953, Charles C Thomas.
103. Saphir, O., Amromin, G. D., and Yokoo, H.: Myocarditis in Viral (Epidemic) Hepatitis, *Am. J. M. Sc.* **231**:168, 1956.
104. Kibrick, S., and Benirschke, K.: Acute Aseptic Myocarditis and Meningoencephalitis in the Newborn Child Infected with Coxsackie Virus, Group B, Type 3. *New England J. Med.* **255**:883, 1956.
105. Terplan, K. L., Constantine, A. B., Koepf, G. F., and Dayton, G. O.: Quoted by Dayton, G. O., Jr.: The Ocular Changes in Thyrotropic Exophthalmos, *Am. J. Ophth.* **36**:1049, 1953.
106. Wright, E. A.: Malignant Exophthalmos Associated With a Fatal Myocarditis, Guy's Hosp. Rep. **106**:36, 1957.
107. Manion, W. C.: Armed Forces Institute of Pathology. Personal communication.
108. Ramos, H., Scalettar, R., and Mattingly, T. W.: Myocarditis Associated With Myositis of the Small Intestine and the Urinary Bladder: Report of a Case. (To be published.)
109. Neustadt, D. H.: Transient Electrocardiographic Changes Simulating an Acute Myocarditis in Serum Sickness, *Ann. Int. Med.* **39**:126, 1953.

The Adams-Stokes Syndrome During Normal Sinus Rhythm and Transient Heart Block. I. The Effects of Isuprel on Patients With the Adams-Stokes Syndrome During Normal Sinus Rhythm and Transient Heart Block

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The purpose of this study was to determine the effects of Isuprel† on patients with Adams-Stokes seizures resulting from ventricular asystole during transient heart block or in the presence of normal sinus rhythm. Isuprel has been found to exert a beneficial effect on patients with syncopal seizures due to carotid sinus cardioinhibitory reflex,^{1,2} and on those in whom cessation of ventricular activity occurred during established atrioventricular block either as a result of ventricular slowing or stoppage^{3,4} or in the course of various forms of ventricular acceleration leading to transient ventricular fibrillation.⁵

It is stated² that the action of this drug consists primarily of an improvement in the general conductivity, so that in some cases a diminution or correction of the atrioventricular block is to be expected, with stimulation and stabilization of the sinus and atrioventricular pacemakers.

In contrast to other epinephrine derivatives, Isuprel is not supposed to increase the blood pressure substantially, nor does the drug tend to initiate ventricular extrasystoles, ventricular tachycardias, or any of the prefibrillatory states.²

More recently, isolated instances have been reported⁶ in which periods of ventricular asystole occurring in the course of normal sinus rhythm were favorably influenced by Isuprel, but after a variable interval an exacerbation of the attacks were no longer controlled by either this drug or any other medicaments. On the contrary, symptomatic relief appeared to have followed the withdrawal of medications when, with the establishment of complete heart block, ventricular asystole no longer developed. It may be worth while to call attention to some phases of the natural course of Adams-Stokes seizures during transient heart block.

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†Isoproterenol hydrochloride.

The Adams-Stokes Syndrome During Normal Sinus Rhythm and Transient Heart Block.—Recent summaries on the Adams-Stokes seizures during established heart block reveal a marked paucity of patients who showed this syndrome during sinus rhythm or transient heart block.⁷ Yet it is very likely that syncopal seizures due to ventricular asystole are much more common in such patients than has been suspected hitherto. Because of the presence of regular sinus rhythm between attacks, these patients are suspected of having other conditions responsible for their symptoms, such as cerebrovascular insults, brain tumors, or even hysterical manifestations. Gilchrist,^{8,9} who has studied this type of paroxysmal ventricular standstill for many years, is under the impression that this syndrome forms a distinct clinical entity, and that such patients react differently in many respects in the development of their seizures than do others who are prone to Adams-Stokes attacks.

Prolonged studies on these patients have revealed at times a very "labile" and unstable state during which attacks of unconsciousness would occur with monotonous regularity, though abruptly and in an unpredictable manner. At times the periods of ventricular asystole would appear only during the sinus rhythm. At other times a period of 2:1 heart block would precede for some time the ventricular stoppage. Yet at other intervals complete heart block was the forerunner of such attacks, only to alternate after a syncopal seizure with sinus rhythm again. No matter what therapeutic measures were instituted, including electrical stimulation of the heart with a pacemaker, they availed only temporarily in aborting these attacks. The intimate factors responsible for these "labile" states are still unknown. At such times the use of Isuprel was often associated with a rapid conversion of the transient heart block, whether complete or partial, to normal sinus rhythm, and the further use of the drug would seem to prevent the return of ventricular asystole. At other times the use of Isuprel resulted in a series of events that precipitated Adams-Stokes seizures or other arrhythmias, so that the medication had to be discontinued. These events were very disturbing and have not been described hitherto. It is this action of Isuprel that we wish to emphasize.

METHOD OF STUDY

Ten patients form the basis of this study. In each instance repeated observations revealed the underlying cardiac mechanism responsible for the syncopal seizures to be asystole of the ventricles, either during transient heart block or in the presence of normal sinus rhythm. All patients were kept in the electrocardiographic circuit for long periods at a time, and records were obtained as often as it was deemed necessary, prior to, during, and subsequent to the use of the drug. All records were taken with standard Lead II only. Between ten to twenty separate observations were carried out on each patient in all stages of the disease.

Blood pressure readings were obtained at stated intervals during normal sinus rhythm as well as during heart block.

The only drug used was Isuprel, as tablets in doses of 10 mg. sublingually, or ampules in doses of 0.2 mg. to each cubic centimeter injected either subcutaneously or intramuscularly. Comparisons were made with the intramuscular injection of epinephrine hydrochloride (1:1000) solution in doses of 1 c.c. under as similar circumstances as was possible in the same patient.

Unless otherwise specified, these studies were carried out with the patients in a semireclining position in bed in order to eliminate the effects of additional postural changes on the cardiac

rhythm. Previous observations had revealed that sitting, standing, and the left and right lateral reclining postures were known to influence the rhythm of the heart in some of these patients. Other experiments were performed with the patients in the sitting posture or standing abruptly from a reclining posture at 5-minute intervals after the use of Isuprel.

Since the type of periodic breathing that is frequently present after Adams-Stokes attacks has likewise been found to influence the rhythm of the heart, only observations obtained during normal respiration were included in the protocols.

Patients with transient heart block due to infection or infarction of the heart or to excessive doses of digitalis bodies were omitted from the study.

RESULTS

The Systemic Effects of Isuprel.—Aside from an occasional intolerance to the drug because of mouth sores and flushing of the face, with mild sweats, tremors, and a sensation of pounding in the chest, the most distressing symptom that followed the use of Isuprel was pulmonary edema. This appeared in only one patient, within from 14 to 20 minutes after the drug was taken sublingually and in less than 5 minutes after its subcutaneous use. In the same patient, pulmonary edema developed after the use of epinephrine hydrochloride. It was obvious from these results that he could not tolerate any of the sympathomimetic drugs. Eventually, because of the increasingly frequent recurrence of Adams-Stokes attacks, he sought admission to another hospital where the use of Isuprel and epinephrine hydrochloride again caused pulmonary edema ending in death.

The Conversion of Heart Block to Normal Sinus Rhythm With Isuprel.—In all ten patients, Isuprel was found to convert either a transient complete or 2:1 heart block, when present, to a normal sinus rhythm, indicating the temporary nature of these cardiac arrhythmias when they appeared after Adams-Stokes seizures. One or two tablets at the most, or 1 c.c. of the solution was sufficient to cause conversion to the normal rhythm. This appeared within from 6 seconds to 20 minutes, as could be judged from the acceleration of both the atrial and ventricular rates, and depended in part on how soon after the presence of heart block the drug was used.

The mechanism of conversion to sinus rhythm took place through the intermediary changes in the pacemakers of the lower centers of the heart, with recurrent shifts from one bundle to another (compare in Fig. 1,A with B, and in Fig. 6,C with D), and with the occasional interposition of beats arising in the A-V node itself. As variations of the QRS complexes continued from dextrograms to levograms with the increase in ventricular rate, supraventricular responses began to appear, at first singly (Fig. 1,F) and then in succession, each one preceded by a normal P-R interval. After the recurrent presence of some forms of interference with dissociation, sinus rhythm replaced the heart block (Fig. 1,I). More often, conversion from heart block to normal sinus rhythm developed through a progressive acceleration of both the atrial and ventricular rates, with the ventricular complexes remaining the same shape, size, and form, indicating their origin on one focus (Fig. 2).

Occasionally, premature beats of the atria and ventricles interrupted the sequence of events, but they were never sufficient in number as compared with

the onset of tachycardias of the ventricles when epinephrine hydrochloride was used on the same patient.

Frequently, the ventricular rate during sinus rhythm was elevated to 160 beats per minute (Fig. 1,*I*) in the conversion from heart block to normal. In the presence of such rapid ventricular rates two patients complained of chest pains, so that the drug had to be discontinued until the tendency for the appearance of these rapid rates had subsided. At times the condition would last for 1 or 2 days after the patients had experienced successive Adams-Stokes seizures over a short period. Anginal seizures were never noted during the slower ventricular rates, so that the action of Isuprel upon the heart was not in itself a factor in the production of pain, as is known to occur with epinephrine hydrochloride.

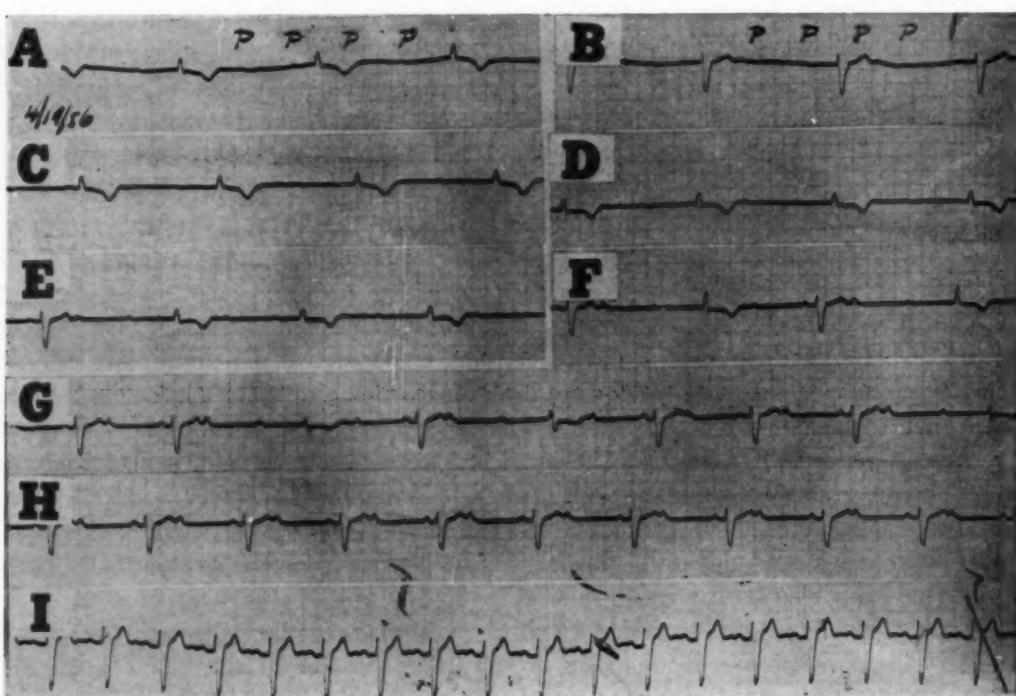


Fig. 1.—Complete heart block after an Adams-Stokes seizure during sinus rhythm converted to sinus rhythm with Isuprel. *A*, Control record, 2:30 P.M.; pacemaker in left bundle. *B*, After Isuprel, 2:46 P.M.; pacemaker in right bundle. *C*, 2:48 P.M. *D*, 2:55 P.M. *E,F,G,H*, 2:58 P.M. to 3:15 P.M. *I*, 4:12 P.M.; sinus rhythm.

Isuprel had no effect upon the rate or rhythm of three patients in whom the block became permanent with ventricular rates averaging 28 beats per minute. In this respect, Isuprel may be used to make a differential diagnosis of the cardiac mechanism underlying Adams-Stokes attacks. A return to normal rhythm is to be expected when the heart block is transient.

Progressive Slowing of the Ventricles With Adams-Stokes Seizures Following the Use of Isuprel.—In two patients, at a time when they were free from syncopal seizures and when their cardiac mechanism revealed a 2:1 heart block, the use

of one tablet of Isuprel resulted in a transitory but further reduction in the ventricular rates. This progressive, enhanced slowing lasting as long as 10 minutes at a time was sufficient to yield syncopal seizures similar to those observed in the natural course of the disease (Table I). For example, the ventricular rate of one patient, at a time when he was free from attacks for at least 12

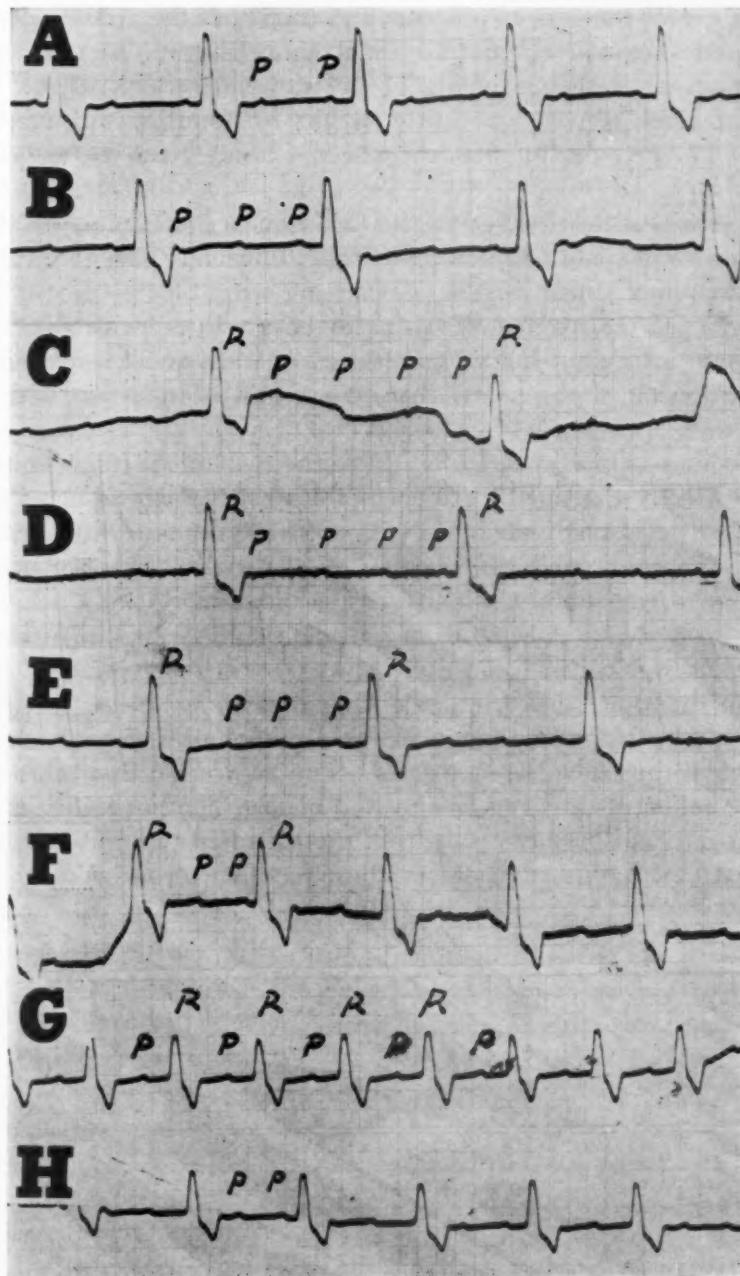


Fig. 2.—Conversion of 2:1 heart block after an Adams-Stokes seizure during sinus rhythm to sinus rhythm through progressive slowing of the ventricular rate. (See Table I.)

hours, averaged 37 beats per minute in the presence of a 2:1 heart block (Fig. 2,A). The atrial rate was 70 beats. Within 1 minute after the use of the drug the ventricles slowed to 30 beats, with the atria averaging 100 beats per minute (Fig. 2,B). Within the next half hour, despite a reduction in the atrial rate to 83.4 beats per minute, there appeared a sudden lowering of the ventricular rate to 20 beats per minute, and syncopal seizures developed (Fig. 2,D). These lasted on and off for the next 10 minutes, and then both the atrial and ventricular rates increased progressively until normal sinus rhythm supervened, 1 hour and 12 minutes after the beginning of the experiment (Fig. 2,G). However, the 2:1 heart block returned abruptly within 10 minutes, and eventually the basic rate of 27 beats per minute reappeared 4 hours after the use of the drug (Fig. 2,H).

Several possibilities are suggested for this sequence of events. In the "labile" state there exists in some of these patients an unusually sensitive carotid sinus cardioinhibitory mechanism in the presence of heart block. Not only could a further slowing of the atria and ventricles be produced with digital pressure over the carotid artery but there also resulted "paradoxical" responses in which, instead of a slowing of the heart, there ensued an acceleration with return to sinus rhythm.

It is said that Isuprel does not influence the systemic pressure substantially.² Yet it is very likely that in the presence of a sensitive carotid sinus mechanism not much of an elevation of the blood pressure within the carotid artery is needed to stimulate the cardioinhibitory reflex. No essential difference was noted in this respect between Isuprel and epinephrine hydrochloride.

Again, in studying the action of atropine sulfate on patients with heart block, attention was called to an early and transitory slowing of the ventricles as a result of the use of this drug, independent of its action on the atrial rate.¹⁰ It was assumed that atropine may act directly upon the vagus nucleus so as to stimulate it and thus slow the ventricles before an acceleration takes place from the blocking action of the drug on the A-V node. The possibility that a somewhat similar mechanism may result from the use of Isuprel must be considered. This may account for its transient inhibitory action on the A-V node so early after its use.

TABLE I

FIG. 2	TIME (P.M.)	RATE		
		atrium	ventricle	
A	8.00	70.5	37.0	Control
B	8.05	100.0	30.0	After Isuprel
C	8.30	83.4	20.0	Syncope
D	8.45	83.4	23.1	Syncope
E	8.50	100.0	25.7	Confused
F	9.00	126.2	45.5	
G	9.35	68.1	68.1	
H	9.55	126.4	50.0	

It has been well known since Erlanger's observations¹¹ and confirmed by others both experimentally and clinically that an acceleration of the atria in the presence of a diseased A-V node may cause a stoppage of the ventricles. This increase in atrial rate must be abrupt, progressive, and need not be more than a few beats in duration in order to fatigue the A-V node very rapidly. Since the atrial rate increased prior to the development of ventricular asystole, this possibility is the likeliest one responsible for the events described.

Sudden Onset of Ventricular Asystole During Sinus Rhythm Due to Supraventricular Tachycardias After Isuprel.—In two other patients, however, who received Isuprel during the early phases of their "labile" state during sinus rhythm in order to prevent the stoppage of the ventricles, the ventricular rate was accelerated abruptly from 80 to 127 beats per minute. The rhythm was at first irregular because of alternate premature beats of the atria, but was soon replaced by a supraventricular tachycardia with a regular rhythm arising, very likely, in the A-V node (Fig. 3,A).

With the onset of this type of tachycardia, there soon developed, at first, isolated blocked atrial beats, and these were followed soon by periods of ventricular asystole of sufficient duration to cause syncopal attacks. This type of irregular heart action lasted for over 3 hours, with Adams-Stokes seizures being registered repeatedly in this interval (Fig. 3,C, D). As the effects of the Isuprel wore off at the end of this period, the rhythm returned to normal at a rate of 80 beats. The use of epinephrine hydrochloride on another occasion resulted in similar changes in this patient.

Ventricular Asystole Occurring in the Upright Posture With Isuprel.—There are a few instances reported in the literature in which a partial heart block (either Type 1 or Type 2) has been found to develop with a change from reclining position to the upright position, and vice versa. Only a few of these give a history of experiencing Adams-Stokes seizures in the upright position. Unfortunately, in none of these was there recorded the alterations in the cardiac mechanism that might have been responsible for these attacks.¹²

In our series of ten patients there were three males and one female who exhibited changes from a normal sinus rhythm to heart block with a change to the upright posture, and in the other two in the reclining posture.

In one patient the repeated use of Isuprel to prevent the development of ventricular asystole resulted in the appearance of complete heart block with a maximum ventricular rate of 50 beats per minute. Despite this rapid ventricular rate during complete heart block, each time he was asked to stand up from a sitting or reclining position, there appeared asystole of the ventricles with Adams-Stokes seizures. When Isuprel was omitted, he merely developed a 2:1 heart block on arising (Fig. 4,E).

Further studies are needed to explain this unusual phenomenon, since hydrostatic changes, a sensitive carotid sinus mechanism, and alterations in the cardiac mechanism due to oxygen want may all play a part in ventricular stoppage at such times. The possibility that Isuprel may sensitize the heart so as to facilitate these changes in the presence of a diseased A-V node must likewise be considered.

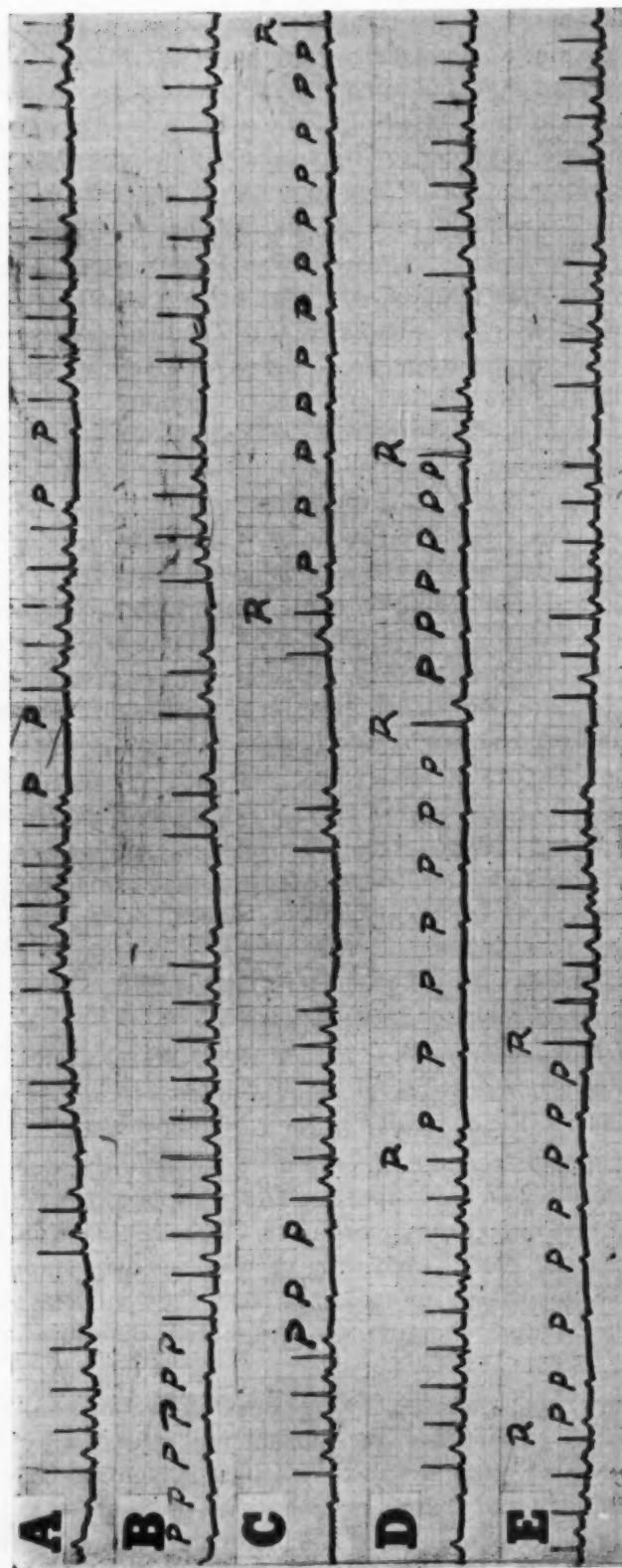


Fig. 3.—Isuprel caused blocked atrial beats followed by recurrent periods of ventricular asystole (B,C,D,E) as a result of the appearance of atrial premature beats and a tachycardia arising in the A-V node.

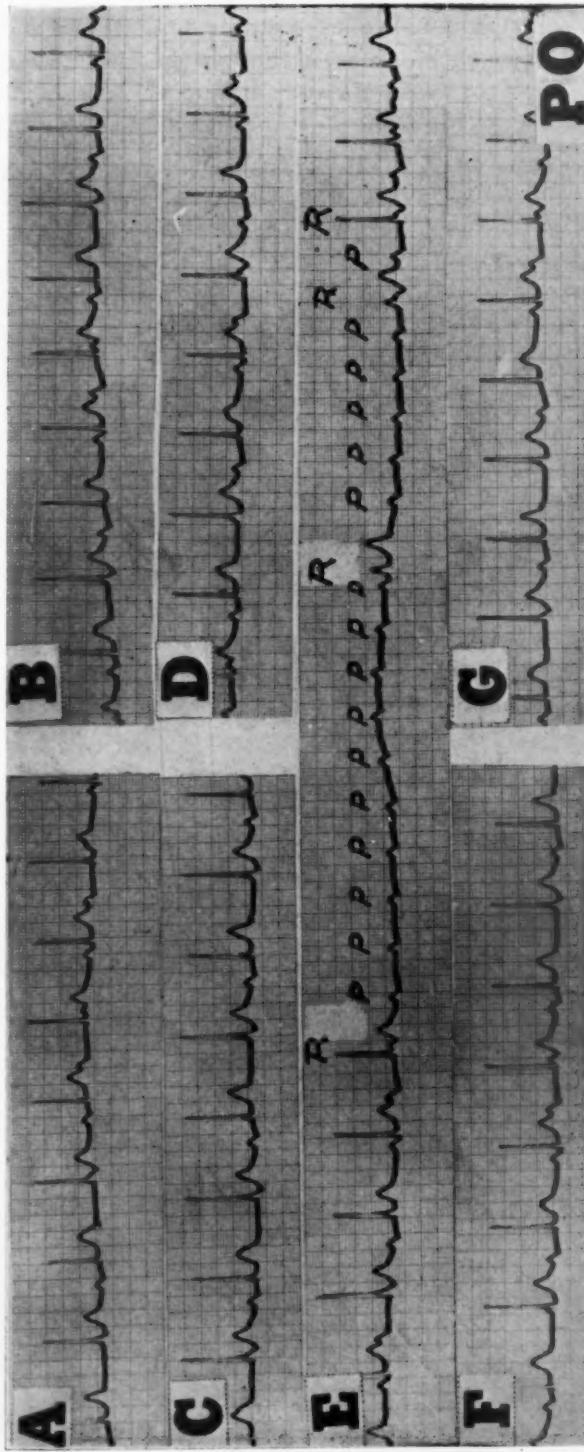


Fig. 4.—Ventricular asystole (E) developing while the patient was in the standing posture after Isuprel had accelerated the ventricles to 50 beats per minute. A, Control in the reclining posture. B, Left reclining posture. C, Right reclining posture. D, Reclining. E, Standing. F, G, Standing.

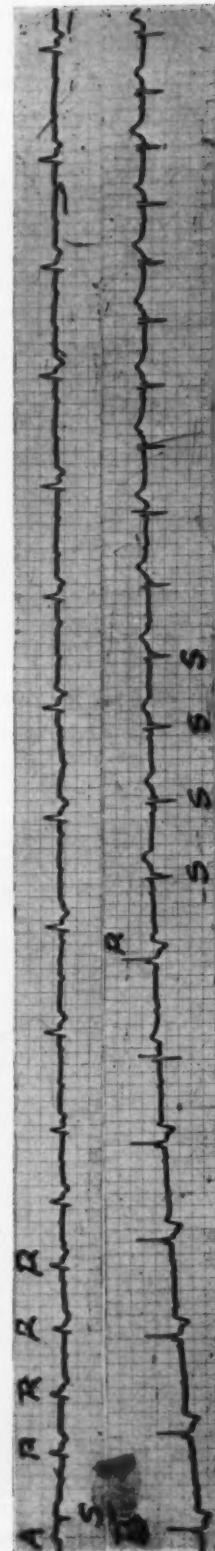


Fig. 5.—Isuprel caused a change in the pacemaker from the left bundle to the right bundle, with progressive slowing of the ventricular rate leading to ventricular asystole. Change from right bundle to left bundle (A), with an acceleration of the ventricular rate to sinus rhythm (B).

Progressive Slowing of the Ventricles With a Change in the Pacemaker of the Bundles of the Heart After Isuprel.—There are some observations that the syndrome of transient heart block with Adams-Stokes seizures may occur more frequently in patients with bundle branch block even though the P-R interval

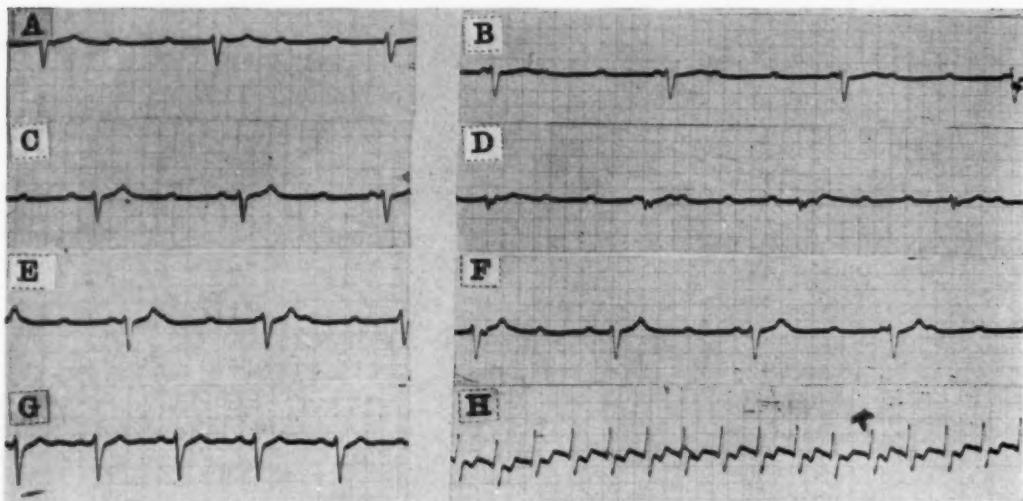


Fig. 6.—Isuprel converted a complete heart block (A) to sinus rhythm (G) followed by atrial flutter.

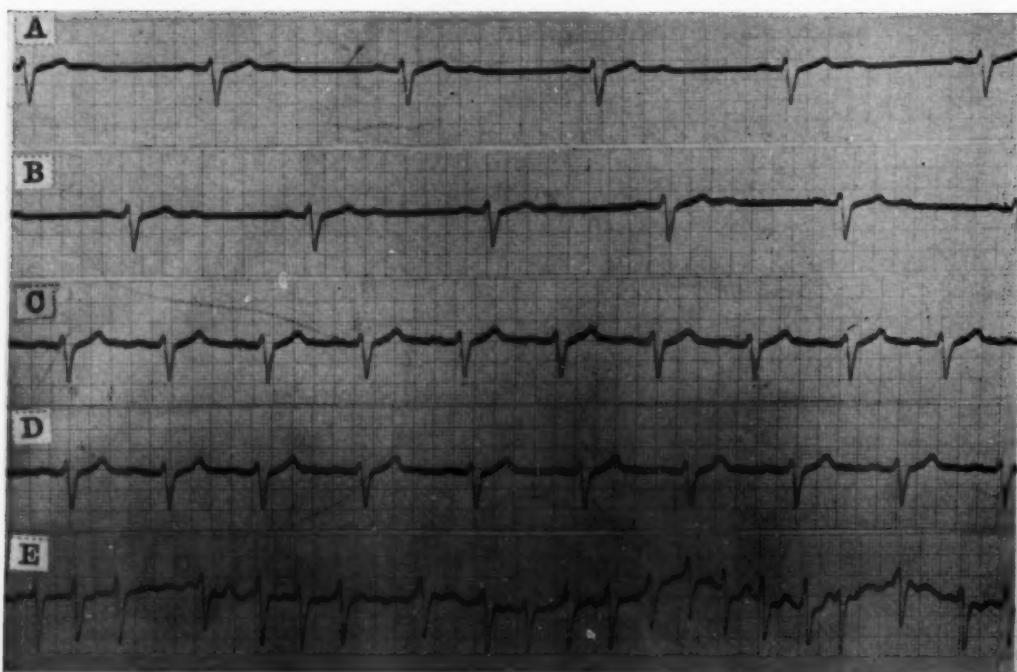


Fig. 7.—Isuprel converted a 2:1 heart block (A) to sinus rhythm (C) and then to atrial fibrillation (E).

may be within normal range. Stokes¹³ is firmly convinced that if a patient gives a history of syncopal attacks and shows in his electrocardiogram the pattern of a bundle branch block with a normal conduction interval, it may be assumed that his seizures are the result of ventricular asystole during transient heart block or in the presence of normal sinus rhythm.

It was pointed out above that in the transition from heart block to normal sinus rhythm, Isuprel stimulated the pacemakers of the heart so that alternating right and left bundle impulses were present before sinus rhythm set in. Stimulation of the right bundle pacemaker by Isuprel in three patients resulted in a progressive slowing of the ventricular rate until ventricular asystole ensued (Fig. 5,A). Conversely, when the left bundle was the predominant pacemaker, as could be judged by changes in the QRS complexes from dextrograms to levo-grams, the ventricles accelerated until sinus rhythm appeared (Fig. 5,B).

Isuprel as a Cause of Atrial Flutter and Fibrillation.—In three patients Isuprel caused the appearance of atrial flutter (Fig. 6,H) or atrial fibrillation (Fig. 7,E) with a rapid ventricular rate when the drug was used in the presence of heart block or sinus rhythm to prevent asystole of the ventricles. The appearance of these arrhythmias was unpredictable, for they occurred in one patient three times after the use of the drug and never again during a period of observation lasting 5 years. Each time the rapid ventricular rate was slowed with digitalis leaf, and conversion to normal followed.

In one patient, atrial flutter appeared in the change from heart block to sinus rhythm after the Adams-Stokes seizures had been present for one-half hour and Isuprel had been given subcutaneously to stop the attacks. In another patient, recurrent periods of atrial flutter interrupted the heart block and disappeared 1 hour after Isuprel had been given sublingually.

DISCUSSION

These observations reveal some unique and "paradoxical" responses to sympathomimetic drugs of patients with Adams-Stokes seizures during normal sinus rhythm or transient heart block. Instead of preventing syncopal attacks due to asystole of the ventricles, these drugs may precipitate them at times. There appears to be no distinction between Isuprel and epinephrine hydrochloride in their action on such patients, except that epinephrine has a tendency to initiate ventricular tachycardias in the transition from heart block to normal rhythm.

Judging from the few necropsies that are available on such patients, it is obvious that each patient has some form of organic disease of the A-V node and its branches due, in most instances, to fibrosis resulting from nutritional disturbances and poor arterial supply to conduction tissues.

The A-V conduction mechanism is a very sensitive neuromuscular structure, yet it must be durable to be able to withstand complete destruction over so many years in some of these patients. It is very likely that an intermittent interference with the blood supply to the bundle branches yields the periodic "lability" during which these patients are subject to ventricular asystole. In this "labile" state the A-V conduction mechanism becomes unusually sensitive to influences that

affect the extrinsic nervous mechanism of the heart. The duration of the stimulus and its intensity are dependent on the state of the A-V node and its branches at any one time. Such a condition may be very fleeting or may last longer. This could account for freedom from seizures for long intervals even in the absence of any medication, a phenomenon well recognized by other students of this subject.¹⁴

Other factors such as deep breathing, changes in posture, exertion, and asphyxial states, as well as drugs, may precipitate or augment these patients' sensitivity. The unpredictable and abrupt development of such influences, which may appear singly or in groups, separately or simultaneously, make the treatment of these patients a difficult task that is well deserving of further studies.

SUMMARY AND CONCLUSIONS

A study was made of the effects of Isuprel on 10 patients who were subject to Adams-Stokes seizures during the presence of sinus rhythm or transient heart block. The action of this drug was compared with that of epinephrine hydrochloride under circumstances as similar as was possible in the same patient.

The development of Adams-Stokes seizures in these patients was found to be associated with an unpredictable "labile" state in which the heart revealed a marked sensitivity to extrinsic nervous responses and other factors that influenced the action of drugs at such times.

Flushing of the face, sweating, mild tremors, and pounding in the chest were some of the systemic manifestations. In one patient, pulmonary edema appeared repeatedly after the use of these drugs.

In all 10 patients it was possible with Isuprel to convert a transient partial or complete heart block to normal sinus rhythm, but in 5 of the 10 patients it was impossible to maintain this rhythm for any length of time with the use of this drug. In this respect, Isuprel may be used to differentiate the cardiac mechanism underlying syncopal attacks in patients with heart block. In those in whom heart block is permanently established, Isuprel may merely accelerate the atrial and ventricular rates without influencing the block.

In 2 patients, at repeated intervals in the conversion from heart block to sinus rhythm, Isuprel caused the appearance of tachycardias of 160 beats per minute. These rapid ventricular rates were associated with anginal seizures that lasted for several hours until the effects of the drug wore off.

In 2 patients, Isuprel caused a progressive slowing of the ventricles from an average of 50 to 20 beats per minute with the onset of Adams-Stokes seizures at a time when the drug was used to convert a 2:1 heart block to normal rhythm. A sensitive cardioinhibitory carotid sinus reflex, acceleration of the atria, or a direct action of Isuprel upon the vagus nucleus are some of the factors to be considered as responsible for these changes at such times.

In 2 patients, Isuprel caused recurrent periods of ventricular asystole with Adams-Stokes seizures as a result of the development of rapid heart rates due to atrial premature beats as nodal tachycardias. The effects of rapid ventricular rates upon a diseased A-V node and its branches is the likeliest explanation for these events.

In 1 patient the abrupt change in posture from a reclining to an upright position caused standstill of the ventricles and Adams-Stokes seizures, even though the drug had increased the ventricular rate during complete heart block to 50 beats per minute.

In the conversion of heart block to sinus rhythm, Isuprel has been found to stimulate the lower pacemakers of the bundles in an irregular manner. In 3 patients, during the "labile" state, the appearance of right bundle branch block was associated invariably with a progressive slowing of the ventricles until asystole supervened. Again, an acceleration of the ventricles with the disappearance of the heart block ensued when the left bundle was stimulated by the drug.

Atrial flutter and atrial fibrillation developed in 3 patients following the use of Isuprel. These arrhythmias appeared during heart block as well as after sinus rhythm had already been established. Digitalis had to be used to abolish the arrhythmias when the ventricular rates were very rapid.

During the "labile" state it was found impossible at times to prevent the appearance of ventricular asystole at the development of Adams-Stokes seizures with any amounts of Isuprel.

The inconstant, unpredictable, and abrupt appearance of such manifestations in patients with Adams-Stokes seizures during the "labile" presence of sinus rhythm and transient heart block is indeed unique and accounts in part for the failure of sympathomimetic drugs to relieve these patients of their symptoms.

When the heart is in a "stable" state, there is no need for the use of any drugs in such patients. Some of these have remained free from seizures without any medication for intervals as long as 5 years.

REFERENCES

1. Nathanson, M. H., and Miller, H.: Circulation **6**:238, 1952.
2. Schaub, F., Holzman, M., and Wyss, S.: Schweiz. med. Wchnschr. **87**:938, 1957.
3. Schumacher, E. E., Jr., and Schmock, C.: Am. HEART J. **48**:933, 1954.
4. Chandler, D., and Rosenbaum, J.: Am. HEART J. **49**:295, 1955.
5. Robben, S. R., Goldfein, S., Schwartz, N. J., and Dack, S.: Am. J. M. Sc. **18**:577, 1955.
6. Jones, R. C.: J.A.M.A. **168**:1840, 1958.
7. Pento, G. B., Miller, H., and Levine, S. A.: Circulation **13**:801, 1956.
8. Gilchrist, A. R.: Brit. M. J. **1**:203, 1937.
9. Gilchrist, A. R.: Scottish M. J. **3**:53, 1958.
10. Schwartz, S. P., and Pool, N.: Am. HEART J. **39**:361, 1950.
11. Erlanger, J.: J. Exper. Med. **7**:676, 1905.
12. Lutembacher, H.: Arch. mal. coeur **12**:145, 1919.
13. Stokes, W.: Brit. Heart J. **9**:267, 1947.
14. Wenckebach, K. F., and Winterberg, H.: Unregelmässige Herzttätigkeit, Leipzig, 1927, William Engelman, p. 395.

Experimental and Laboratory Reports

Clinical Evaluation of a New Esophageal Electrode, With Particular Reference to the Bipolar Esophageal Electrocardiogram

Part I. Normal Sinus Mechanism

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According to a principle first enunciated almost 70 years ago by Waller,¹ the scope of conventional clinical electrocardiography may be seriously limited by the fact that it is restricted to the registration of differences in potential produced on the surface of a volume conductor by an electrical generator contained within the volume conductor. In order to circumvent these limitations it has been common practice in fundamental research electrocardiography to record direct epicardial and transmembrane potentials in open-chest preparations.²⁻⁵ These techniques have also been applied successfully to human beings at the time of open-chest surgery.⁶⁻⁹

Percutaneous epicardial electrocardiography, however, would probably be too hazardous for common clinical use. The great veins and the bronchial lumina offer a relatively safe pathway for approaching the heart, but their use for this purpose requires a somewhat complicated and time-consuming technical procedure.

On the other hand, the esophagus offers a relatively harmless and convenient route for introducing a sensing electrode into the juxtacardiac region of the electrical field produced by the heart. Furthermore, although the region avail-

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able to the esophageal electrode is relatively limited, it is a region which may be comparatively "blind" in the conventional electrocardiographic lead combinations.

The first known esophageal electrocardiogram was recorded in 1906, by Cremer,¹⁰ who passed a 10 by 1.5-cm. electrode into the esophagus of a professional sword swallower. Most of the published reports on esophageal electrocardiography have dealt with results obtained by the "unipolar" technique.^{11-14,16-20,22-62} However, in 1935, Luisada^{14,16} reported a study of bipolar esophageal electrocardiograms (i.e., electrocardiograms obtained by recording the difference in potential between two metallic electrodes located 1 cm. apart in the esophageal lumen). Following Luisada's²¹ review article on the subject in 1940, the bipolar esophageal technique was virtually abandoned until Kistin and Bruce³¹ called attention to some of its possible merits in a recent publication.

During the past several years in this laboratory we have been actively interested both in advanced concepts of heart-lead relationships and in the development of a simple but effective salt-bridge technique⁶³ for the registration of unipolar esophageal leads. It occurred to us that these two fields of interest might be united profitably in the development of a systematic study of the principles and clinical usefulness of bipolar esophageal electrocardiography.

Accordingly, we developed a new type of bipolar esophageal electrode in which were incorporated the desirable features of the previously described unipolar electrode.⁶³ During the past 18 months this electrode has been employed on 100 occasions in a systematic study of 96 subjects. The fundamental principles evolving from this project have been described in a companion paper.⁶⁴ In the present report we deal with the findings derived from the study of 26 subjects with normal sinus rhythms. We employ here the underlying principles together with purely empirical observations, in what is essentially a clinical evaluation of bipolar esophageal electrocardiography.

METHODS AND MATERIALS

The bipolar esophageal electrode is constructed from a standard, soft-rubber Miller-Abbott tube* (see Fig. 1). It consists, in essence, of a 150-cm. length of double-lumen tubing with a lead of No. 32 stainless steel suture wire running the length of each lumen and anchored into a specially constructed plastic obturator tip. A side opening, 1 mm. in diameter, is punched into each lumen near the distal end of the assembly. The longitudinal distance between the centers of these two holes is 2 cm., and they are oriented approximately 180 degrees apart (see Fig. 2).

When in use, each lumen of the electrode assembly is filled with physiologic saline solution. Under these circumstances each of the punched-out side openings, filled with saline solution, serves as a pickup electrode. The resistance of each of these electrodes is approximately 750 ohms.

The metallic connector assembly with which the original Miller-Abbott tube is provided is of considerable value in the construction of the esophageal lead. This assembly is separated into its individual components by applying a hot soldering iron to it. The pieces of metallic tubing are employed to complete the proximal end of the esophageal lead. Inserted into the respective proximal ends of the lumina, they serve as anchors to which the stainless steel lead wires are soldered. Since they also accept the male end of a standard two-way hypodermic syringe valve, they are quite useful in filling the lumina with saline solution, and then maintaining the desired column of the solution.

*Size 16-Fr., Bittner, New York, N. Y.

We employed a direct-writing, four-channel electrocardiograph* routinely in this study. A special auxiliary unit was constructed which contained a Wilson central terminal (composed of three matched 68,000-ohm resistors) and a lead selector switch. This unit also provided a cable to each of the four extremities of the patient, a connection to each of the two esophageal lead terminals, and an input cable to each of the four electrocardiographic channels. The potentials at the proximal and distal members of the esophageal electrode pair were recorded as unipolar leads in the "A" and "B" channels, respectively; the difference in potential between the two electrodes was recorded as a bipolar esophageal lead in the "C" channel; and the desired Einthoven lead (usually Lead II) was recorded in the "D" channel. The bipolar esophageal connection was so arranged that an upward deflection of the tracing occurred when the proximal electrode was more positive than the distal electrode.

The standard clinical procedure was, first, to anesthetize lightly the nasopharynx on the desired side with a pernasal spray of 2 per cent Pontocaine hydrochloride solution. The subject was instructed to hold his breath while the nose was being sprayed, and then to swallow any material which accumulated in the back of the throat. No more than 1 c.c. of anesthetic solution was employed in any of the procedures; no instances of drug reaction occurred.

The esophageal electrode was then passed and advanced until the midpoint of the esophageal electrode pair reached the desired distance beyond the nares. Since the study of atrial electrical activity was the purpose of this study, this distance was usually about 47 cm. Thus, in many individuals the electrode assembly was not introduced into the esophagus to a depth sufficient for thorough study of the ventricles.

RESULTS IN NORMAL SINUS MECHANISM

Among the multichannel, multilevel esophageal lead surveys which we performed, 10 subjects (Group I) had neither historical nor clinical evidence of heart disease. A typical survey of Group I is shown in Fig. 3, which demonstrates many of the salient features of both unipolar and bipolar esophageal leads.

As the esophageal electrode is withdrawn in steps of 1 cm., the unipolar tracings (rows VE_P and VE_D) exhibit the normally expected metamorphosis.^{18,19,25-27} The bipolar tracings, however, exhibit a decidedly different type of progression, which, as will be shown later, forms the basis for certain uniquely valuable diagnostic properties of the bipolar lead.

Inspection of the bipolar tracings (row BE) indicates that the main deflection of the atrial complex rather abruptly reverses direction between the 39- and 40-cm. levels. We designate this region of abrupt reversal, which is seen to be intimately associated with the unipolar transitional form, as the level of *bipolar atrial transition*. We find that this type of bipolar transition, with the atrial complexes predominantly positive below, invariably occurs in subjects with a sinus mechanism. In general, bipolar transition is located as critically as shown in Fig. 3, although occasionally a 2-cm. increment in the location of the tube is required to pass through transition.†

As explained in the companion paper,⁶⁴ the prime requisite for bipolar transition is that the wave of atrial activation reach both electrodes of the esophageal

*Sanborn Poly-Viso, Sanborn Company, Waltham, Mass.

†Fig. 3 also shows a secondary bipolar atrial transition between the 41- and 42-cm. levels. This type of transition is not intimately associated with the level of unipolar atrial transition; it fails to occur in some subjects with a normal sinus mechanism; and it appears thus far to possess no special clinical diagnostic importance. Therefore, no further reference will be made to it in this report.

lead at the same time. Furthermore, the configuration of the atrial complex to either side of transition reflects relative phase lag in the arrival of atrial activation at the respective member electrodes of the lead assembly. Accordingly, bipolar esophageal leads recorded from the transitional region should be critically sensitive to even minor alterations in the time course of atrial depolarization. This prediction was substantially confirmed by observations on subjects with disordered atrial mechanisms.

Another potentially valuable diagnostic property of the bipolar esophageal lead lies in its ability to augment P-wave amplitude while minimizing the QRS deflection. This property is best illustrated in Lead BE-39 of Fig. 3, in which it is seen that the peak-to-peak amplitude of the atrial deflections is approximately five times that of the ventricular complex. The prospective special merit of this situation should be the relative simplicity of sorting atrial from ventricular deflections when they happen to occur simultaneously. This has not only proved to be the case but we have usually found it possible in such circumstances to distinguish between normal sinus beats and atrial impulses which are either retrograde or ectopic.

An additional 16 subjects (Group II) had a normal sinus mechanism throughout their esophageal lead surveys, but presented evidence for some other type of cardiac abnormality. All of the subjects in Group I fell within the semivertical and vertical categories of electroposition. In Group II the electroposition ranged from horizontal to vertical. The importance of the electrical position of the heart in determining the configuration of the esophageal ventricular complex has been noted.^{26,34,43}

Postero-anterior and lateral roentgenograms of the chest were made in 10 subjects of Group I and 4 subjects of Group II with the esophageal electrode assembly located at the level of bipolar atrial transition. These films were reviewed by a senior radiologist who interpreted them as showing the midpoint of the esophageal electrodes in apposition to the left atrium in all instances. It was the radiologist's further impression that the electrode was located at the same level as the left atrial center of gravity in 8 subjects, 1 cm. above in 1 subject, 2 cm. above in 1 subject, 1 cm. below in 2 subjects, and 2 cm. below in 2 subjects. These observations, interpreted in terms of the pertinent heart-lead relationships,⁶⁴ indicate that bipolar esophageal leads recorded from the vicinity of atrial transition provide virtually pure proximity electrograms of the left atrium.

In order to correlate the bipolar esophageal lead with the unipolar and extremity leads, measurements were made at the level of bipolar atrial transition (transitional), 4 cm. above this level (supraregional), and 4 cm. below the transitional level (infratransitional). Measured in detail were: (1) P-wave amplitude, (2) QRS-complex amplitude, (3) P-wave duration, (4) P-R interval, (5) atrial phase lag (relative delay in onset of P waves in the esophageal leads as compared to Lead II), and (6) time of onset of the atrial intrinsicoid deflection as measured from the beginning of atrial deflection. These data are presented in Table I. It is apparent that the atrial transitional level, recorded in centimeters from the nares, was similar in the two groups, in both unipolar and bipolar leads.

As anticipated, Table I shows that the amplitude of atrial deflection is much greater at all three levels of the esophageal leads than it is in Lead II. In addition, the atrial deflections tend to be larger in the bipolar esophageal leads than in the unipolar. At the infratransitional levels the unipolar atrial deflections are relatively small and tend to assume a rounded contour without a well-de-

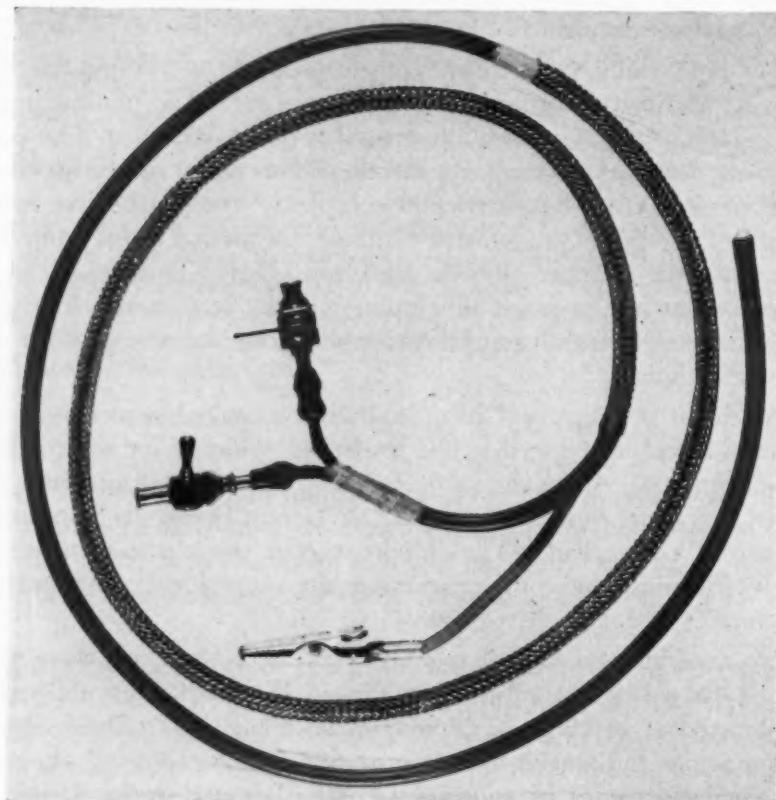


Fig. 1.—Photograph of the bipolar esophageal lead assembly which is constructed from double-lumen gastrointestinal tubing. The illustration shows the specially constructed plastic obturator, and the more distal of the two side openings. The proximal portion of the assembly is covered with braided metallic shield in order to minimize the possibility of electrical interference from power lines, etc. Further description in text.

← 2 cm. →

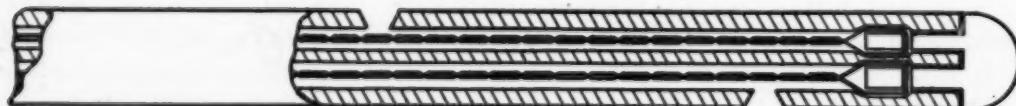


Fig. 2.—Construction detail of the distal end of the esophageal lead assembly. A loop of stainless steel wire runs throughout the length of each lumen of the tubing, and is anchored in the plastic obturator tip. In use, each lumen is filled with a column of physiologic saline solution. Each of the small, saline filled side openings serves as a pickup electrode.

marcated intrinsicoid deflection, indicating a loss of proximity effect. At suprarectal levels there is also some reduction of amplitude, but the loss of proximity effect is less marked.

Table I also shows that the duration of the atrial deflection is significantly less in both unipolar and bipolar esophageal leads than it is in Lead II. A corollary observation is that the onset of atrial deflection occurs significantly later in the esophageal leads than in Lead II. These findings are compatible with the proximity-lead concept of esophageal tracings, and are therefore in accord with Brown's^{18,19} observations that esophageal leads rather closely approximate direct epicardial registration from the atrium.

As shown in Table I, unipolar esophageal leads produce some magnification of the peak-to-peak QRS deflections as compared to Lead II, but even greater magnification of P deflections. Therefore, the P:QRS ratio is considerably greater in the unipolar esophageal leads than in the extremity leads. This is simply a way of stating in numerical terms that unipolar esophageal leads render the atrial complex easily visible.

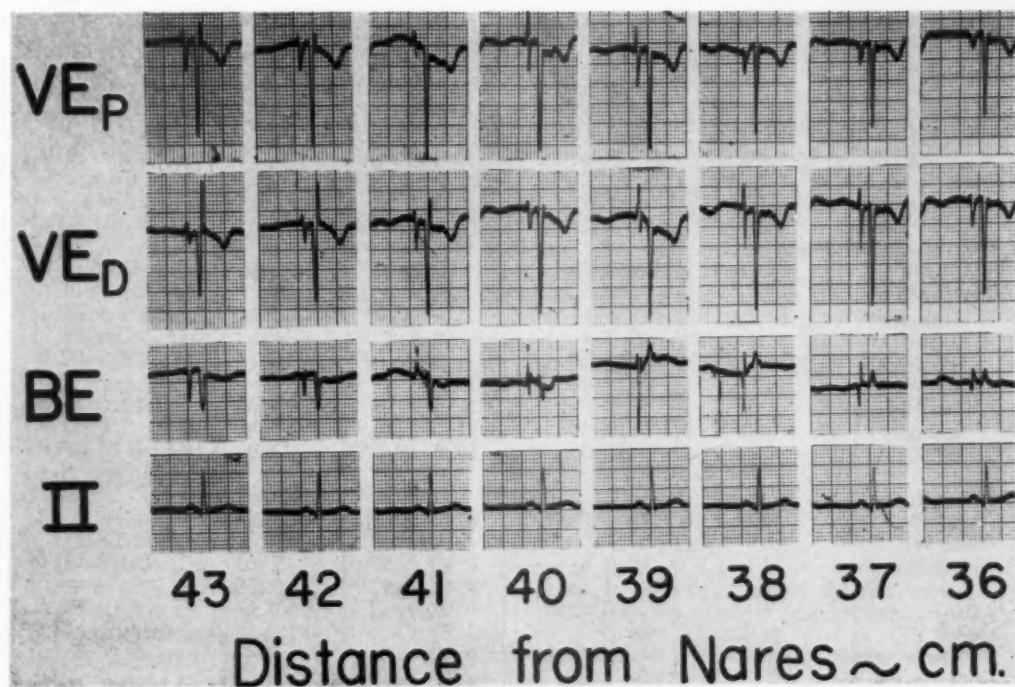


Fig. 3.—A typical multichannel, multilevel esophageal lead survey obtained from a normal subject. The four leads were recorded simultaneously. Excess material has been trimmed away, and the cuttings remounted in correct temporal alignment. Further description and discussion in text.

Application of the same numerical index to the bipolar esophageal leads indicates that they possess this property to an even greater degree than do the unipolar esophageal leads. At the optimum level of registration the P:QRS ratio ranges from 1 to 7 (average = 2.7), as compared to mean values of 0.10 and 0.07 in Lead II of Groups I and II, respectively. Despite the near-cancellation

of ventricular deflections produced by the bipolar technique, it was nevertheless not difficult to recognize the QRS deflections in all of the subjects of Groups I and II. In dealing with arrhythmias, bipolar registration at various esophageal levels was occasionally required to distinguish between atrial and ventricular deflections.

TABLE I. COMPARATIVE ANALYSIS OF THE TIME AND AMPLITUDE RELATIONSHIPS BETWEEN BIPOLAR ESOPHAGEAL (BE) LEADS, UNIPOLAR ESOPHAGEAL (VE) LEADS, AND LEAD II

MEASUREMENT	GROUP I (10 PATIENTS)		GROUP II (16 PATIENTS)	
	MEAN	RANGE	MEAN	RANGE
Age (years)	24	13-32	43	15-88
Transitional Level (cm.)				
Lead BE	37	31-41	36	30-41
Lead VE	35.4	28-39	—	—
P-Wave Amplitude (mm.)				
Lead II	1.02	0.5-1.5	0.72	0.2-1.0
Lead BE				
Transition	7.0	2.5-20.0	7.0	1.0-17.0
Supratriansition	4.1	2.0-7.0	5.5	2.0-16.0
Infratriansition	3.5	1.0-7.5	5.1	0.5-8.0
Lead VE				
Transition	8.0	4.0-12.5	8.25	3.0-19.0
Supratriansition	19.5	13.0-26.5	18.5	9.0-32.5
Infratriansition	4.4	1.5-7.5	11.4	2.0-9.0
QRS Amplitude (mm.)				
Lead II	10.9	8.0-16.0	12.4	3.0-23.0
Lead BE				
Transition	6.3	2.0-19.0	8.1	0.5-36.0
Supratriansition	2.8	1.0-5.0	4.6	2.0-12.0
Infratriansition	14.6	3.0-32.0	16.5	2.0-50.0
Lead VE				
Transition	24.5	16.5-31.5	23.8	10.0-47.5
Supratriansition	19.5	13.0-26.5	18.6	9.0-32.5
Infratriansition	27.0	10.5-40.0	27.9	10.5-48.0
P:QRS Ratio				
Lead II	0.096	0.04-0.15	0.072	0.02-0.12
Lead BE				
Transition	1.65	0.42-6.67	2.61	0.08-15.0
Supratriansition	1.81	0.67-4.00	1.59	0.33-4.00
Infratriansition	0.379	0.03-1.33	0.663	0.04-2.33
Lead VE				
Transition	0.343	0.12-0.58	0.412	0.07-1.93
Supratriansition	0.271	0.065-0.80	0.381	0.03-1.60
Infratriansition	0.175	0.07-1.43	0.246	0.06-0.80

The time of onset of the intrinsicoid deflections was measured in the esophageal leads, and the phase relationships between them calculated. Although the phase differences in the onset of intrinsicoid deflections are numerically small, they are of considerable theoretical and practical importance. When the onset of the intrinsicoid deflection in the proximal unipolar lead precedes that in the distal lead by a slight time interval, the main atrial deflection in the bipolar

esophageal lead is a sharp negative spike with a very short time base. Conversely, reversal of the phase relationship in the unipolar lead produces a sharp positive atrial spike in the bipolar lead. Consequently, the direction and relative amplitude of the atrial spike in the bipolar lead are intimately related to the phase relationships between the unipolar atrial complexes, and for this reason depend upon the direction of the atrial impulse at each level of registration. Accordingly, the direction and amplitude of the bipolar atrial spike, especially when recorded

TABLE I. COMPARATIVE ANALYSIS OF THE TIME AND AMPLITUDE RELATIONSHIPS BETWEEN BIPOLAR ESOPHAGEAL (BE) LEADS, UNIPOLAR ESOPHAGEAL (VE) LEADS, AND LEAD II—CONT'D

MEASUREMENT	GROUP I (10 PATIENTS)		GROUP II (16 PATIENTS)	
	MEAN	RANGE	MEAN	RANGE
P-Wave Duration (sec.)				
Lead II	0.07	0.04-0.08	0.08	0.04-0.12
Lead BE				
Transition	0.05	0.02-0.08	0.05	0.03-0.07
Supratransition	0.05	0.03-0.07	0.045	0.03-0.06
Infratransition	0.05	0.02-0.09	0.05	0.01-0.08
Lead VE				
Transition	0.06	0.04-0.08	0.06	0.025-0.105
Supratransition	0.065	0.045-0.08	0.06	0.04-0.08
Infratransition	0.06	0.04-0.075	0.06	0.02-0.09
P-R Interval (sec.)				
Lead II	0.14	0.10-0.17	0.17	0.16-0.20
Lead BE				
Transition	0.12	0.08-0.16	0.13	0.09-0.17
Supratransition	0.12	0.08-0.14	0.13	0.10-0.16
Infratransition	0.12	0.11-0.14	0.13	0.08-0.19
Lead VE				
Transition	0.12	0.10-0.145	0.13	0.055-0.17
Supratransition	0.13	0.085-0.16	0.14	0.10-0.18
Infratransition	0.12	0.09-0.135	0.135	0.095-0.18
P-Wave Phase Lag (sec.) (Esophagus vs. Lead II)				
Lead BE				
Transition	0.03	0.01-0.07	0.05	0.03-0.10
Supratransition	0.03	0-0.05	0.04	0-0.08
Infratransition	0.02	0-0.04	0.04	0-0.07
Lead VE				
Transition	0.02	0.01-0.06	0.04	0.015-0.075
Supratransition	0.02	0-0.04	0.03	0-0.07
Infratransition	0.03	0.01-0.045	0.03	0-0.065
Onset Time of Intrinsicoid Deflection (sec.)				
Lead BE				
Transition	0.03 (7)*	0.01-0.06	0.03 (12)	0-0.05
Supratransition	0.03 (9)	0.02-0.04	0.03 (13)	0.01-0.06
Infratransition	0.03 (6)	0.01-0.08	0.02 (16)	0.01-0.04
Lead VE				
Transition	0.03 (10)	0.02-0.05	0.035 (16)	0.015-0.055
Supratransition	0.03 (6)	0.015-0.05	0.03 (12)	0.015-0.045
Infratransition	0.02 (7)	0.01-0.03	0.03 (12)	0.01-0.06

*Number of patients are given in parentheses.

near the transitional level, tend to be critically responsive to ectopic beats. In the case of retrograde impulses the bipolar atrial spike tends to reflect the anticipated reversal of phase relationship between the unipolar leads.

Deviations of the P-R segment of as much as 2.0 mm. above or below the base line were frequently demonstrated in the bipolar leads in both groups of subjects. These deviations were associated with only minor deviations from the base line (of the P-R segment) in the standard body surface leads.

A great deal has been written concerning the wave of atrial repolarization⁶⁵⁻⁸⁰ (called T_a wave by most authors, after Hering⁶⁵). Although this wave could be detected frequently in the bipolar esophageal leads of many subjects in this series, the T_a wave was not amplified to a degree even approaching the magnification of atrial depolarization deflections. (A well-defined T_a wave is shown in Fig. 3, BE-40 to BE-42.) In those tracings with nearly complete cancellation of QRS the T_a wave was neither consistently demonstrable nor was it unusually well demarcated.

DISCUSSION

The bipolar esophageal lead is simply a time-based record of the difference in potential between the two member electrodes of the lead assembly. In essence, therefore, it is the algebraic difference, $VE_p - VE_d$, between the two unipolar leads. Theoretically, it should contain no information which is not inherently present in simultaneous registration of the two unipolar leads. From the practical point of view, however, we find that the bipolar esophageal lead does possess considerable special merit. This situation is highly comparable to the special diagnostic merit, in posterior myocardial infarction, of Lead III (which is Lead II - Lead I) and/or Lead aVF (which is Lead II - $\frac{1}{2}$ Lead I), as compared to Leads I and II alone.

Two salient features of the bipolar esophageal lead have already been pointed out. One of these is its ability to produce near-cancellation of the ventricular deflections while at the same time augmenting the amplitude of the atrial deflections. This property makes it easy to sort atrial deflections from ventricular deflections when the two of them occur simultaneously. The other salient feature is the occurrence of a critically located level of atrial transition, with its attendant uniform property, in sinus mechanisms, of the atrial deflection being predominantly positive below the level of transition and predominantly negative above transition. Since both the occurrence of transition itself and the predictable order of atrial wave morphology through transition are critical indicators of phase relationships at the two esophageal electrodes, the bipolar lead provides a sensitive means of detecting alterations in the time course of atrial depolarization. In general, we have found that information of this type is much more readily apparent in the bipolar than in the simultaneously recorded unipolar esophageal leads. Ectopic atrial contractions could be recognized by bipolar registration in some situations in which their morphology in the unipolar esophageal leads was essentially the same as that of sinus beats.

In developing the bipolar lead assembly described here we had some misgivings because the two sensing electrodes were, in effect, located on opposite

sides of a structure that was 5 mm. in diameter. Fortunately, this circumstance did not seem to interfere with the desired function and reliability of the device.

Luisada^{14,15,21} believed the bipolar lead to be optimal for the study of left atrial activity, and it now seems well established that esophageal leads are semi-direct electrograms of the left atrium. However, mostly on the basis of lead-field considerations, we doubt Luisada's claim that a tongue-to-xiphoid lead possesses genuine specificity for the registration of right atrial activity.

Apparently, an esophageal electrode located in the vicinity of atrial transition is insensitive to the initial and terminal forces of atrial depolarization. Lacking complete information, we find it difficult to reconstruct the exact anatomic and electrical relationships responsible for this situation, but it is almost certainly the correct interpretation of the delayed onset and short time base of unipolar esophageal P waves as compared to the P waves of Lead II. The same consequences are reflected, of course, in the bipolar esophageal leads.

The time of onset of the atrial intrinsicoid deflection in this series was significantly shorter than has been reported previously. The mean time of onset of the intrinsicoid deflection in all esophageal electrodes was 0.03 second in both our groups of normal sinus mechanisms, at all three of the positions analyzed (range, 0.01 to 0.08 second; see Table I). Kistin and associates²⁶ reported a time of onset of the intrinsicoid deflection in the atrial complex of 0.03 to 0.08 second, with a mean of 0.056 second. Hecht²³ gives an average value of 0.05 second in normal individuals for the interval from the onset of P in Lead V₁ to the onset of the intrinsicoid deflection in the simultaneously recorded atrial esophageal leads. Enselberg²⁸ reported intrinsicoid deflections occurring from 0.04 to 0.06 second after the beginning of atrial activity. On the other hand, Foster and Thayer⁶⁶ report esophageal P waves with a duration of less than 0.04 second, implying a more rapid onset of intrinsicoid deflection than was observed by us. We are unable to account for these differences.

The sizable base-line deviations of the P-R segment which we observed in our normal subjects pose some interesting questions, since deviations of comparable magnitude occurring in the extremity leads have been offered as a criterion for the diagnosis of atrial infarction, both experimental^{62,70,81-83} and clinical.^{67,68,72,74-76,79,84} Similar P-R deviations in extremity leads have also been ascribed to arterial hypertension⁶⁹ and pulmonary emphysema.⁸⁰ The duration of the P-T_a interval, as is the case with the Q-T interval, depends upon the heart rate, and normally varies from 0.15 to 0.45 second.⁸⁵ Therefore, the initial portion of the P-T_a segment forms the P-R segment. Accordingly, early onset of the T_a deflection, such as appears in the report of Sprague and White,⁶⁶ in 1924, may cause apparent deviation of the P-R segment in normal subjects. The occurrence of such deviations might well be the atrial counterpart of the so-called early repolarization phenomenon which has been described in connection with ventricular activity. When P-R deviations of this genre occur in esophageal leads, we feel that they must almost certainly be reflected in the extremity leads, but with much less magnitude because of the loss of proximity effects in the extremity leads.

REFERENCES

1. Waller, A. D.: Phil. Trans. Roy. Soc., London, B. **180**:169, 1889.
2. Lewis, T., Meakins, J., and White, P. D.: Phil. Trans. Roy. Soc., London, s.B. **205**:375, 1914.
3. Puech, P., Esclavissat, M., Sodi-Pallares, D., and Cisneros, F.: AM. HEART J. **47**:174, 1954.
4. Sodi-Pallares, D., and Calder, R. M.: New Bases of Electrocardiography, St. Louis, 1956, The C. V. Mosby Company, pp. 55-59.
5. Lutembacher, R.: Arch. mal. coeur **45**:1099, 1952. (Abstract in Circulation **8**:621, 1953.)
6. Woodbury, J. W., Lee, J., Brady, A. J., and Merendino, K. A.: Circulation Res. **5**:179, 1957.
7. Barbato, E., Pileggi, F., Debes, A. C., Fujioka, T., Magalhães, M. S., Tranches, J., San Juan, E., and Décourt, L. V.: AM. HEART J. **55**:867, 1958.
8. Barbato, E., Fujioka, T., Debes, A. C., Pileggi, F., Filho, C. B., Paula e Silva, P., and Décourt, L. V.: AM. HEART J. **56**:340, 1958.
9. Brusca, A., Solerio, F., and Actis-Dato, A.: AM. HEART J. **57**:134, 1959.
10. Cremer, M.: München. med. Wchnschr. **53**:811, 1906.
11. Baur, L.: Deutsches Arch. klin. Med. **145**:129, 1924.
12. Lieberson, A., and Liberson, F.: Proc. Soc. Exper. Biol. & Med. **31**:441, 1934.
13. Scherf, D., and Siedek, H.: Ztschr. klin. Med. **127**:77, 1934.
14. Luisada, A.: Klin. Wchnschr. **14**:160, 1935.
15. Luisada, A.: Cuore e circolaz. **19**:77, 1935.
16. Howard, F. H.: AM. HEART J. **10**:833, 1935.
17. DeChatel, A., and Hussey, R.: Ztschr. klin. Med. **131**:450, 1936.
18. Brown, W. H.: AM. HEART J. **12**:1, 1936.
19. Brown, W. H.: AM. HEART J. **12**:307, 1936.
20. Spühler, O.: Ztschr. klin. Med. **134**:671, 1938.
21. Luisada, A.: J. Lab. & Clin. Med. **25**:1146, 1940.
22. Wuensche, H. W.: Deutsches Arch. klin. Med. **186**:358, 1940.
23. Hecht, H. H.: Proc. Central Soc. Clin. Res. **16**:56, 1943.
24. Schwartz, M.: Northwest Med. **46**:448, 1947.
25. Wenger, R.: Cardiologia **13**:248, 1948.
26. Kistin, A. D., Brill, W. D., and Robb, G. P.: Circulation **2**:578, 1950.
27. Oblath, R., and Karpman, H.: AM. HEART J. **41**:369, 1951.
28. Enselberg, C. D.: AM. HEART J. **41**:382, 1951.
29. Steinberg, M. F., Kroop, I. G., and Grishman, A.: J. Mt. Sinai Hosp. **18**:337, 1952.
30. Friese, G.: Arch. Kreislaufforsch. **22**:288, 1955. (Abstract in Circulation **15**:140, 1957).
31. Kistin, A. D., and Bruce, J. C.: AM. HEART J. **53**:65, 1957.
32. Rubin, I. L., Jagendorf, B., and Goldberg, A. L.: AM. HEART J. **57**:19, 1959.
33. Hamilton, J. G. M., and Nyboer, J.: AM. HEART J. **15**:414, 1938.
34. Nyboer, J.: AM. HEART J. **22**:468, 1941.
35. Helm, J. D., Jr., Helm, G. H., and Wolferth, C. C.: AM. HEART J. **27**:755, 1944.
36. Burchell, H. B.: Am. J. M. Sc. **216**:492, 1948.
37. Oram, S., Holt, M., and East, T.: Brit. Heart J. **13**:475, 1951.
38. Burchell, H. B., and Pruitt, R. D.: AM. HEART J. **42**:81, 1951.
39. Bain, C. W. C.: Brit. Heart J. **13**:485, 1951.
40. Elek, S. R., Lawrence, M. H., and Griffith, G. C.: Circulation **7**:656, 1953.
41. Rubin, I. L., Margolies, M. P., Smelin, A., and Rose, O. A.: AM. HEART J. **46**:38, 1953.
42. Scherlis, L., Wener, J., Grishman, A., and Sandberg, A. A.: AM. HEART J. **41**:246, 1951.
43. Godfrey, J.: Ann. West. Med. & Surg. **6**:214, 1952.
44. Evans, E., and Black, T. C.: Am. Rev. Tuberc. **61**:335, 1950.
45. Wenger, R., and Wick, E.: Arch. Kreislaufforsch. **17**:246, 1951. (Abstract in Circulation **6**:294, 1952.)
46. Bengtsson, E.: Cardiologia **21**:141, 1952.
47. Nazzi, V., and Morassuti, P.: Cuore e circolaz. **37**:271, 1953. (Abstract in Circulation **11**:148, 1955.)
48. Myers, G. B., and Klein, H. A.: AM. HEART J. **35**:727, 1948.
49. Scherlis, L., and Grishman, A.: J. Mt. Sinai Hosp. **18**:149, 1951.
50. Harvey, A. McG.: Ann. Int. Med. **11**:57, 1937.
51. Nyboer, J., and Hamilton, J. G. M.: Brit. Heart J. **2**:263, 1940.
52. Kossmann, C. E., and Berger, A. R.: Ann. Int. Med. **15**:128, 1941.
53. Youmans, W. B., Goodman, M. J., and Gould, J.: AM. HEART J. **37**:359, 1949.
54. Franke, H.: Ztschr. klin. Med. **146**:171, 1950.
55. Grishman, A., Kroop, I. G., Jaffe, H. L., and Steinberg, M. F.: (Abstract) Am. J. Med. **8**:395, 1950.
56. Foster, R. F., and Thayer, R. H.: AM. HEART J. **40**:224, 1950.
57. Kistin, A. D., and Landowne, M.: Circulation **3**:738, 1951.
58. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E.: The Auricular Arrhythmias, Springfield, Ill., 1952, Charles C Thomas, Publisher.
59. Wenger, R., and Hofmann-Credner, D.: Circulation **5**:870, 1952.
60. Schrire, V., and Vogelpoel, L.: AM. HEART J. **49**:162, 1955.

61. Wenger, R., and Wick, E.: *AM. HEART J.* **49**:116, 1955.
62. Wenger, R., Massumi, R. A., and Kuramoto, K.: *Cardiologia* **26**:193, 1955.
63. Brody, D. A., Harris, T. R., and Romans, W. E.: *AM. HEART J.* **50**:923, 1955.
64. Brody, D. A., and Copeland, G. D.: *AM. HEART J.* **57**:3, 1959.
65. Hering, H. E.: *Pflügers Arch. ges. Physiol.* **144**:1, 1912.
66. Sprague, H. B., and White, P. D.: *J. Clin. Invest.* **1**:389, 1924.
67. Hahn, L., and Langendorf, R.: *Acta med. scandinav.* **100**:279, 1939.
68. Langendorf, R.: *Acta med. scandinav.* **100**:136, 1939.
69. Hahn, L.: *Brit. Heart J.* **2**:101, 1940.
70. Cushing, E. H., Feil, H., Stanton, E. J., and Wartman, W. B.: *Brit. Heart J.* **4**:17, 1942.
71. Feil, H.: *J. Mt. Sinai Hosp.* **8**:502, 1942.
72. Young, E. W., and Koenig, A.: *AM. HEART J.* **28**:287, 1944.
73. Miller, R., and Perelman, J. S.: *AM. HEART J.* **31**:501, 1946.
74. Roberts, J. T., and Loube, S. D.: *AM. HEART J.* **34**:188, 1947.
75. Hellerstein, H. K.: *AM. HEART J.* **36**:422, 1948.
76. Soderstrom, N.: *Acta med. scandinav., Suppl.* **217**:7, 1948.
77. Slapak, I.: *Cardiologia* **22**:228, 1953.
78. Friesse, G.: *Ztschr. Kreislaufforsch.* **43**:159, 1954. (Abstract in *Circulation* **11**:299, 1955.)
79. Gross, D.: *AM. HEART J.* **50**:24, 1955.
80. Wasserburger, R. H., Ward, V. G., Cullen, R. E., Rasmussen, H. K., and Juhl, J. H.: *AM. HEART J.* **54**:875, 1957.
81. Abramson, D. I., Fenichel, N. M., and Shookhoff, C.: *AM. HEART J.* **15**:471, 1938.
82. Sanders, A.: *Am. J. M. Sc.* **198**:690, 1939.
83. Corsi, V., Sangiorgi, M., and Corelli, D.: *Cardiologia* **23**:255, 1953.
84. Di Ielsi, A. J., Pinsky, H. A., and Eynon, H. K.: *Ann. Int. Med.* **36**:640, 1952.
85. Lepeschkin, E.: *Modern Electrocardiography*, Vol. I.: *The P-Q-R-S-T-U Complex*, Baltimore, 1951, Williams & Wilkins Company.
86. Shipley, R. A., and Hallaran, W. R.: *AM. HEART J.* **11**:325, 1936.
87. Stewart, C. B., and Manning, G. W.: *AM. HEART J.* **27**:502, 1944.

Clinical Evaluation of a New Esophageal Electrode, With Particular Reference to the Bipolar Esophageal Electrocardiogram

Part II. Observations in Cardiac Arrhythmias

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In previous reports from this laboratory^{1,2} we described a relatively simple and reliable method for recording esophageal electrocardiograms, and developed a body of fundamental principles which pertain specifically to this particular branch of electrocardiography. Part I³ of the present communication describes certain technical advances which permit registration of bipolar as well as unipolar esophageal tracings. It also contains a report on detailed studies of atrial activity in normal and abnormal subjects with normal sinus mechanism. In this section of the study we present our findings in cardiac arrhythmias, as culled from 74 multilevel, multichannel esophageal lead surveys which exhibited one or more types of mechanism disorder.

The various abnormalities encountered are listed according to category in Table I. The left-hand column of Table I lists the number of records according to the one diagnosis which was considered to be of primary interest in each record. The right-hand column includes the records of all disorders, and shows that 169 records of such disorders were encountered.

Premature ventricular contractions comprised one fourth of all abnormal mechanisms, and was the primary diagnosis in 14 out of 74 records. Retrograde conduction to the atria was recognized in 9 of 42 instances of premature ventricular beating. The bipolar esophageal lead proved helpful in recognizing retrograde conduction because of the features of phase discrimination and augmented P:QRS ratio described in Part I³ of this report. From an opposite point of view, the bipolar lead prevented an erroneous diagnosis in a subject who showed a P wave sandwiched between an antecedent ventricular premature beat and a ventricular beat with apparent aberrant conduction: The diagnosis of a

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reciprocal ventricular beat was initially considered, but the bipolar esophageal lead showed that the interposed atrial beat almost undoubtedly originated at the sinoatrial node.

As might be expected, the conventional electrocardiogram alone sufficed for the quick and accurate diagnosis of many abnormal mechanisms. In other instances, in which the correct diagnosis was suspected from the conventional leads, the esophageal leads provided strong confirmatory evidence. In still other cases the essential diagnostic information was contained only in the esophageal leads. In this latter group the bipolar esophageal lead tended to be more informative than the unipolar, but not invariably so. In order to give some perspective of the relative merits of conventional and esophageal leads in subjects with interesting or unusual arrhythmias, a number of illustrative examples are presented below, together with pertinent comments. In each example the various leads (VE proximal, VE distal, bipolar esophageal leads, and Einthoven Lead II or III) were recorded simultaneously and remounted in their original temporal alignment after excess material had been trimmed away.

Fig. 1 illustrates a case of atrial bigeminy in which the diagnosis is readily discernible in all of the leads. However, an additional and unexpected finding, which is apparent with certainty only in the bipolar esophageal lead, is the occurrence of electrical alternans of the QRS complexes. We interpret this as

TABLE I. CLASSIFICATION OF MECHANISM DISORDERS ENCOUNTERED IN 100 ESOPHAGEAL LEAD SURVEYS

MECHANISM DISORDER	PRIMARY DIAGNOSIS (CASES)	TOTAL NUMBER OF DIAGNOSES (CASES)
Sinus tachycardia	5	12
Atrial premature beats	11	17
Atrial premature beats, blocked	—	1
Atrial bigeminy	—	4
Atrial tachycardia	1	1
Atrial flutter	5	5
Atrial fibrillation	14	15
Reciprocal beats (atrial)	4	6
Wandering pacemaker	2	7
Ventricular premature beats	14	42
Ventricular bigeminy	—	3
Ventricular parasystole	—	2
Ventricular tachycardia	2	5
Retrograde conduction	—	9
Retrograde block	—	1
1° A-V block	1	4
2° A-V block	4	11
Wenckebach phenomenon	—	5
3° A-V block	6	6
A-V dissociation	1	1
Nodal premature beats	1	4
Nodal rhythm	—	2
Nodal tachycardia	1	3
Wolff-Parkinson-White syndrome	1	1
Electrical alternans	1	2
Total	74	169

indicating that slight aberration of intraventricular conduction occurs in association with each beat of extrasinus origin. Furthermore, the unipolar esophageal lead, VE-43, shows two interesting features which appear worthy of special mention: (1) There is significant depression of the P-R segments which follow atrial beats, P_e , of sinus origin. This suggests that the atria are exhibiting the phenomenon of so-called early repolarization, perhaps related to the extrasystolic compensatory pauses. (2) The time base of the atrial premature beats, P_e , is 0.12 second or longer, as compared to a normal average value of 0.05 second in our series. This suggests that the premature atrial impulses encounter a sort of "intra-atrial block." In order to explain this observation we do not feel obliged to invoke the existence of specialized conducting tissue in the atria; rather,

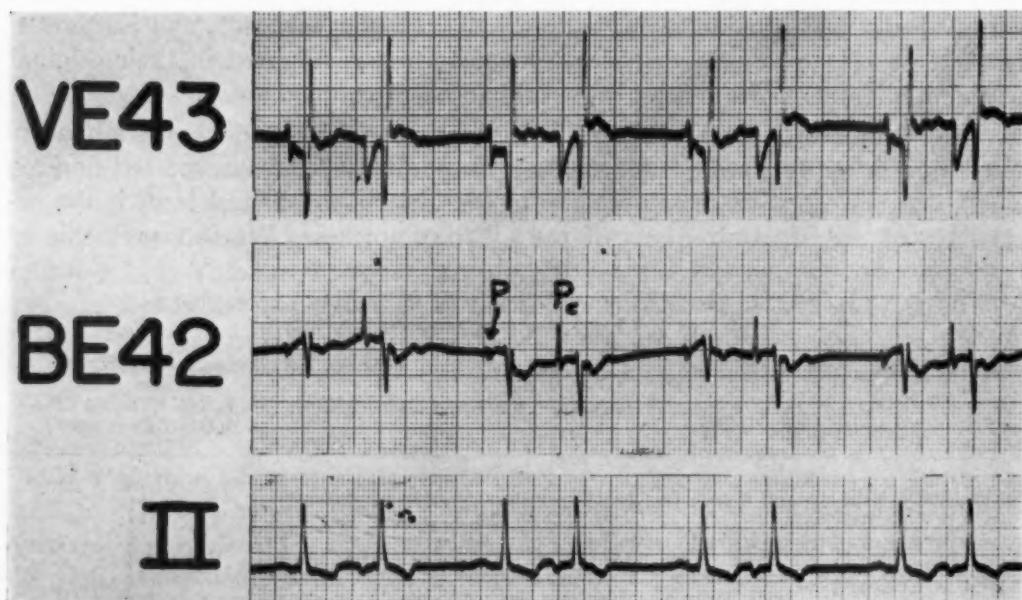


Fig. 1.—A case of atrial bigeminy which, in addition to the basic arrhythmia, illustrates electrical alternans of the ventricular complexes, intra-atrial "block," probable early repolarization phenomenon of the atria, and large T_a deflections. Further discussion in the text.

we feel that the broadening of the P_e waves is due more likely to a combination of an irritable focus in one portion of the atria, with delayed spread of the atrial impulse due to relatively slow recovery of irritability in other portions of the atria. Following each of the atrial extrasystoles, VE-43 shows considerable elevation of the S-T segment take-off. This could be related to the aberration of intraventricular conduction, but it is at least equally likely that it is due to the occurrence of a sizable T_a deflection.

Fig. 2 is an interesting example of two ectopic atrial beats, P_{x1} and P_{x2} , emanating from different foci. This diagnosis is evident in all esophageal leads, but in Lead II, while the second ectopic beat is readily recognized, the first ectopic beat is buried in the preceding T wave without appreciably altering its contour.

Therefore, on the basis of a routine Lead II rhythm strip alone the QRS complex which follows P_{x1} might be erroneously diagnosed as a premature nodal beat. This possibility for error was obviated by use of the esophageal lead.

Fig. 3 is an example of atrial tachycardia (rate 176 per minute) with first degree A-V block and occasional blocked A-V conduction followed by a relatively short P-R interval. This tracing is of special interest because of the bizarre QRS complex, apparent only in the bipolar esophageal lead, which follows each episode of blocked atrioventricular conduction. The special peculiarity of each of these bizarre complexes consists of a tremendous exaggeration, R_{ab} , of the terminal, positive spike as compared to the relatively small terminal, positive spike which is present in the remainder of the QRS complexes. Because

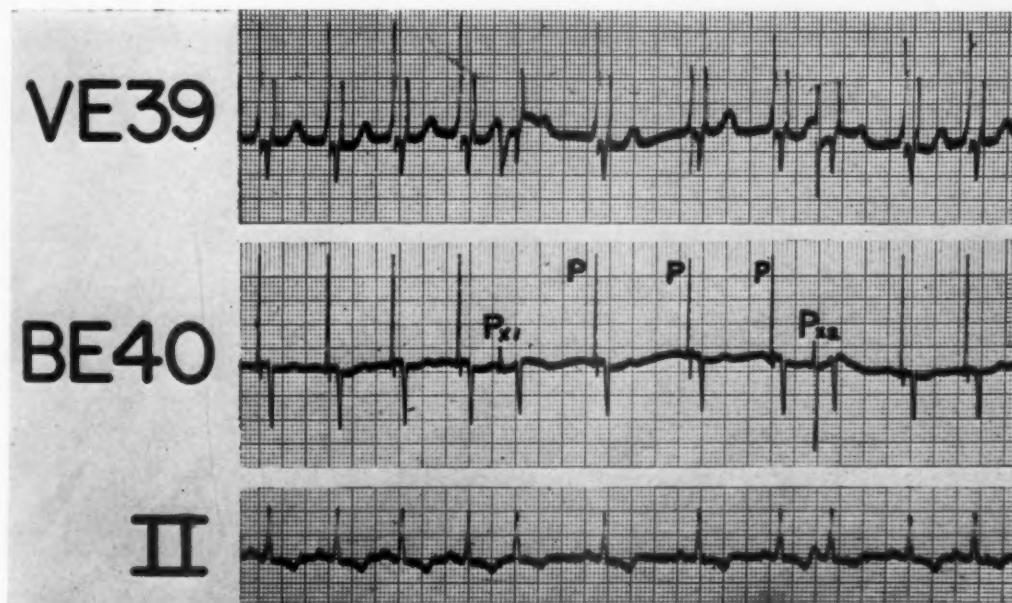


Fig. 2.—Ectopic atrial beats (P_{x1} and P_{x2}) which emanate from two different foci. The second ectopic beat is clearly recognizable in Lead II, whereas the first one is not. The possibility of erroneously diagnosing the latter as a nodal premature beat is avoided by use of the esophageal lead technique.

of the nearly exact spacing between the three R_{ab} spikes (2.16 seconds between the first and second, and 2.20 seconds between the second and third) it is tempting to entertain a possible diagnosis of atrial paroxysm in this case. Another possibility is that, following each of the shortened P-R intervals, a period of supernormal conduction occurs at a time which is appropriate for accepting a re-entrant impulse from the atrioventricular junctional tissue. If this interpretation were correct, the R_{ab} spikes of Fig. 3 would represent reciprocal atrial beats. However, it seems most likely to us that the R_{ab} spikes represent aberrant intraventricular conduction following each of the blocked ventricular beats.

Fig. 4 is a rather classic example of atrial flutter with an atrial rate of 340 beats per minute, and a 2:1 block of atrioventricular conduction. The bipolar

esophageal lead illustrates this mechanism disorder in a particularly striking manner since all electromotive activity except that due to atrial depolarization is virtually cancelled out, leaving a residue of relatively huge flutter waves (f). This example is fairly typical of our cases of atrial flutter, indicating that this type of disorder is characterized by a large number of atrial depolarization forces acting in concert. In contrast, atrial fibrillary activity observed in esophageal leads frequently is not of much greater amplitude than that recorded in the precordial leads V₁ and V₂. This observation is in accord with the concept that the depolarization forces in atrial fibrillation occur in a disorganized, segmental fashion, rather than in unison.

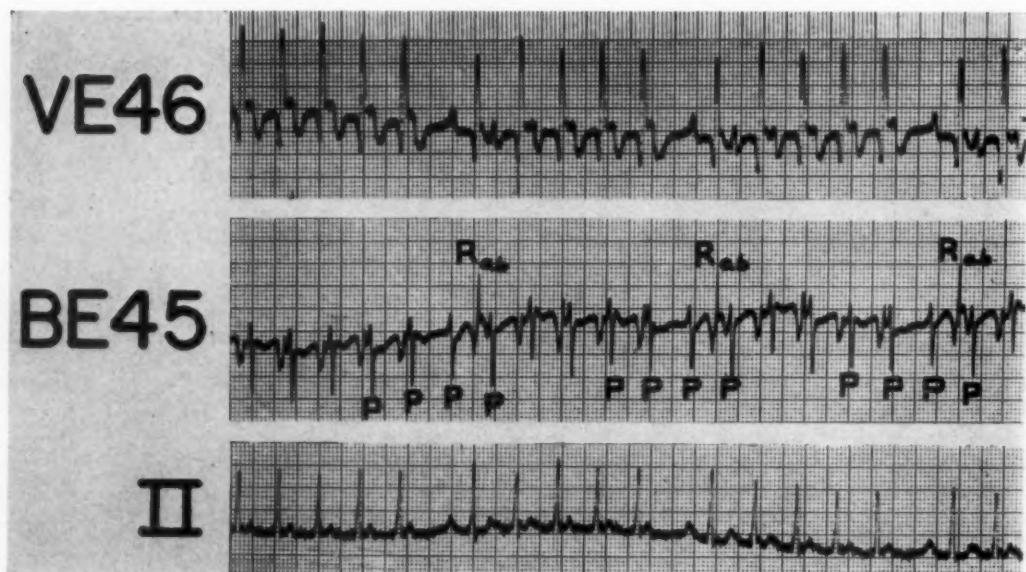


Fig. 3.—A case of atrial tachycardia with first degree atrioventricular block and an occasional nonconducted impulse. The P-R interval after each of the nonconducted impulses is relatively short, and is followed by a bizarre ventricular complex which is characterized by the occurrence of a large, positive, terminal spike, R_{ab} . In the text several possible explanations of these bizarre QRS complexes are discussed, but it seems most likely that they represent aberrant intraventricular conduction.

Fig. 4 poses some interesting questions regarding the nature of the repolarization forces in atrial flutter. It is rather remarkable that the T_a waves are essentially of the same magnitude in Lead III as in the unipolar esophageal leads, even though the latter are proximity leads. We believe this is due to the fact that repolarization does not occur as a propagated impulse, but rather as a diffuse process which, for each segment of atrial myocardium, is spread out over a long period of time as compared to local passage of the depolarization process. Since atrial flutter is a rapid mechanism, total repolarization must occur relatively quickly, producing a sizable T_a deflection in the extremity leads. On the other hand, because the repolarization front is broad and diffuse, it does not produce a strikingly large deflection in the unipolar esophageal lead. In the example shown in Fig. 4 the repolarization process affects both unipolar eso-

phageal electrodes almost identically with respect to amplitude and phase, producing virtual cancellation of the T_a deflection in the bipolar esophageal tracing. This suggests that in atrial flutter the atrial repolarization process may not pursue the same anatomic course as the wave of depolarization, and consequently the electrical gradient of the atria is not necessarily zero.

In Fig. 5, reading from left to right, one observes five normal P-QRS sequences. The remainder of the record shows three sequences of reciprocal atrial beating. Each sequence is initiated by a premature atrial beat, P_x , which is followed after a prolonged transmission time by a ventricular response of unaltered form. Each of these three ventricular beats is followed rather promptly by a retrograde (reciprocal) atrial beat, P_r . In this illustration the retrograde nature of the reciprocal beats is strikingly apparent from the reversed direction of the P_r spikes in the bipolar esophageal leads. An additional atrial ectopic beat, P'_x , is seen which does not produce a reciprocal beat because there has been adequate time for recovery of the junctional tissue.

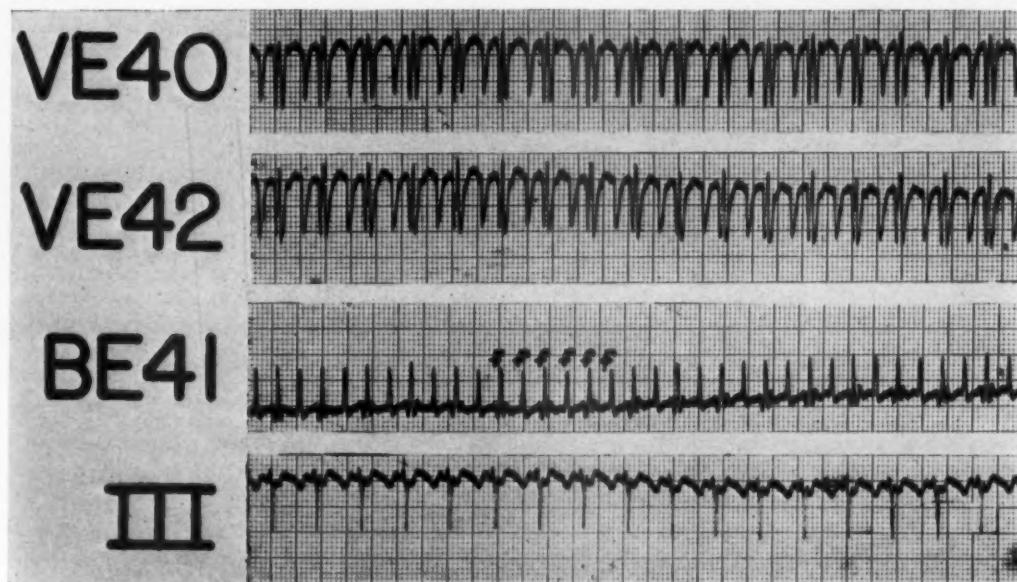


Fig. 4.—A classic example of atrial flutter in which the flutter waves, f , are demonstrated most strikingly in the bipolar esophageal lead. As discussed in the text, an analysis of the various leads presented here seems to shed some significant light on the nature of the atrial repolarization forces in flutter, as well as the depolarization forces.

Fig. 6 shows a case of nodal tachycardia with retrograde atrial beats. The alternative interpretation of sinus or atrial tachycardia with prolonged P-R interval is excluded by other portions of the record in which short periods of complete asystole are followed directly by the characteristic QRS-P sequence shown in Fig. 6. Furthermore, we observed a reversal of the normal order of changes in P-wave morphology as the esophageal electrode was withdrawn through the level of bipolar atrial transition. As explained earlier, this circumstance alone strongly suggests the diagnosis of retrograde atrial beats.

In contrast to the unipolar esophageal leads, the bipolar tracing, BE-34, depicts rather clearly the nature of the final atrial beat, P_x , which appears in the illustration. Without the help of the bipolar esophageal tracing one might be tempted to conclude that the pacemaker had shifted temporarily from a "low" to a "high" or "mid" nodal site. Lead BE-34, however, shows a complete reversal of the final atrial spike, P_x , thus making it reasonably certain that the final atrial beat is of supranodal origin even though it is superimposed on the terminal portion of the QRS complex.

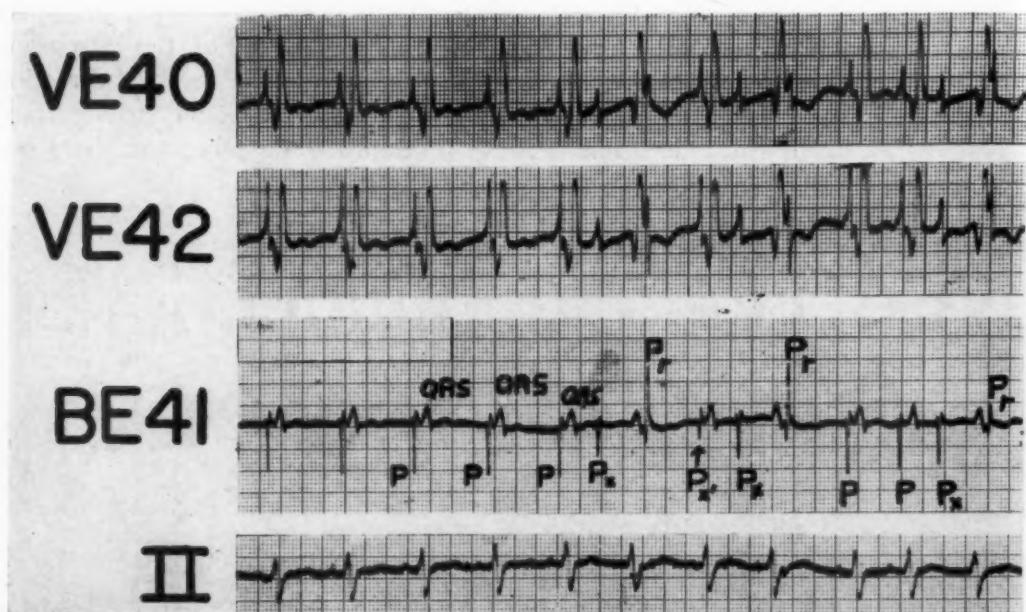


Fig. 5.—Illustration of three reciprocal beats of the atrium (P_x -QRS- P_r , "sandwiches") which are initiated by ectopic atrial beats. A fourth ectopic beat, P_s' , fails to elicit a reciprocal atrial response because it happens to be only slightly premature. Further discussion in text.

Fig. 7 illustrates the occurrence of retrograde atrial beats, P_r , in a case of complete antegrade atrioventricular block. We observed that retrograde atrioventricular conduction occurred in this subject only when the preceding P-R interval fell somewhere within the range of 0.35 to 0.40 second. This observation indicates that the phenomenon of retrograde conduction probably depends upon the development of a transient phase of supernormal excitability. It should be remarked that this is one example in which an interesting and rather unusual atrial disorder is displayed more vividly in the unipolar than in the bipolar esophageal leads. On the other hand, the bipolar leads present the T_a deflection more clearly than it appears in the unipolar leads. It should also be added that the correct diagnosis was not convincingly evident in the conventional electrocardiogram, although it was unmistakable in a high-fidelity electrocardiogram recorded at 75 mm. per second.

Fig. 8 is considered to be an instance of ventricular tachycardia with 2:1 block of retrograde (ventriculo-atrial) conduction. The subject was a 63-year-old

white man who suddenly developed a regular tachycardia of 186 beats per minute 3 weeks after an acute posterior myocardial infarction. This is an especially good example of cancellation of ventricular complexes in the bipolar esophageal

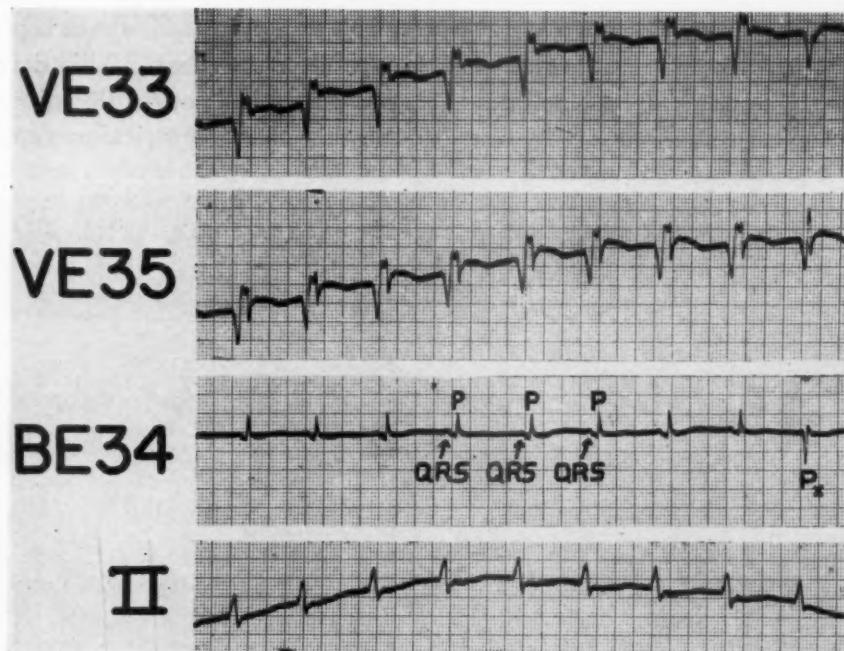


Fig. 6.—Nodal tachycardia with retrograde conduction (recorded at a paper speed of 50 mm. per second). In this example the bipolar esophageal electrocardiogram is particularly valuable in establishing that the final atrial complex, P_* , is of supranodal rather than "mid" or "high" nodal origin.

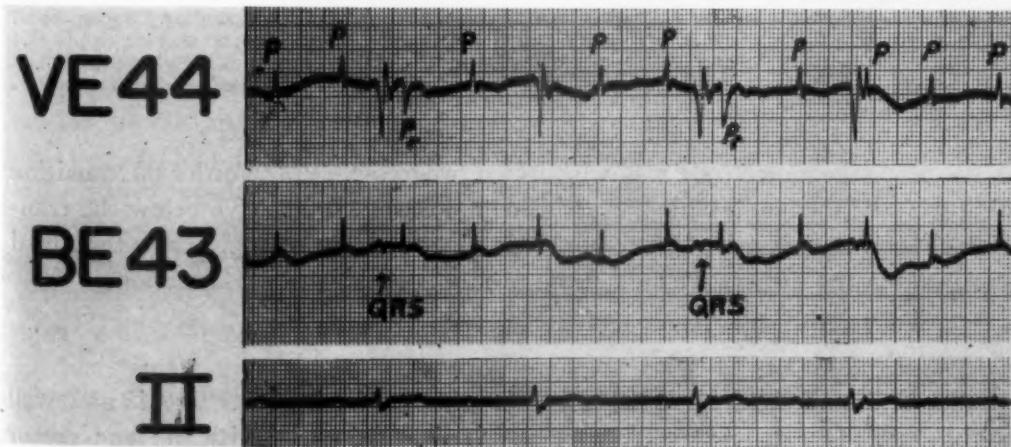


Fig. 7.—A case of complete antegrade atrioventricular block with occasional retrograde, P_r , conduction to the atria. On conventional electrocardiography this case was originally diagnosed erroneously as complete A-V block with positive chronotropism. However, the correct diagnosis was clear on a Lead II rhythm strip recorded on a high-fidelity electrocardiograph at a paper speed of 75 mm. per second.

lead, although this particular feature of itself does not add significantly here to the ease of diagnosis. The conventional electrocardiogram shows wide ventricular complexes and a small, notched deflection superimposed on the ascending limb of every other beat. The esophageal leads confirm the impression that the notching represents atrial activity. The bipolar esophageal lead shows a positive deflection of 0.36 second's duration following each atrial beat. This deflection is probably due to atrial repolarization (T_a wave) and is most readily discernible in the bipolar lead because of the near-cancellation of the ventricular complexes.

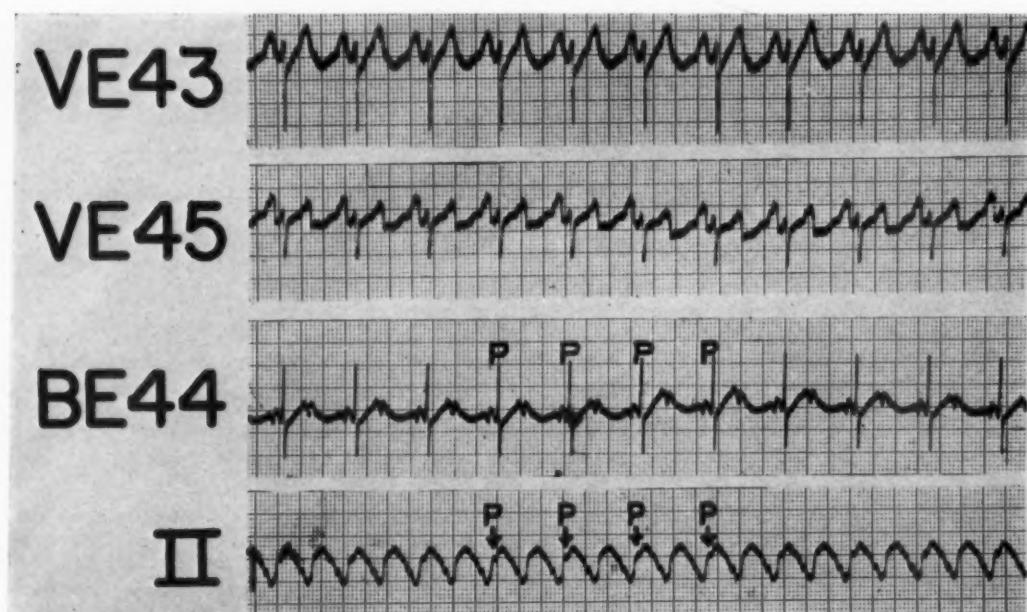


Fig. 8.—A case of ventricular tachycardia with 2:1 block of retrograde (ventriculo-atrial) conduction. In this example the bipolar esophageal lead, as compared with the corresponding unipolar leads, adds nothing material to the ease or correctness of the diagnosis. However, the bipolar esophageal lead does show sizable T_a deflections which are not clearly recognizable in any other of the leads, and might therefore be of some special value if the clinical significance of the atrial repolarization forces were better understood.

As the esophageal electrode was withdrawn progressively, the order of transition was reversed; that is, the bipolar atrial complexes were negative below the transitional level and positive above it. This suggests very strongly that the atrial complexes in the subject are indeed the product of retrograde conduction.

DISCUSSION

The value of esophageal leads for studying cardiac arrhythmias is now well established. In the preceding report² which dealt primarily with the lead-vector and lead-field principles as they apply to the interpretation of esophageal electrocardiograms, the bipolar esophageal lead was shown to possess two unique properties of special clinical value: (1) In recording from the level of atrial transition it is strikingly sensitive to even minor variations in the time course

of atrial depolarization. (2) It greatly facilitates determination of the timing and direction of atrial activation in situations in which such information ordinarily would be obscured by the concomitant occurrence of ventricular depolarization. The illustrations shown are presented as evidence of the clinical value of this lead in arrhythmias, both simple and complex.

The marked variation in morphology of the ectopic atrial beats shown in Figs. 1 through 3 exemplifies the special sensitivity of the bipolar lead to such events. In our cases of atrial flutter, in addition to accentuation of P with simultaneous diminution of QRS, the bipolar lead also tended to cancel the large undulations attributable to T_a waves.

Reciprocal beating, a fascinating and uncommon arrhythmia, consists of an impulse re-entry occurring after the impulse presumably has followed a circuitous pathway through the atrioventricular junctional tissue. The hypothetical circumstances required to produce reciprocal beats have some recent experimental confirmation in the study of Moe and associates⁴ on the dual nature of transmission through the junctional tissue. Animal experiments more than 25 years ago showed that in certain circumstances, parts of the conduction system of the frog's heart may allow orthograde conduction, whereas in other parts, only retrograde conduction is possible.^{5,6} Classically, the sequence of reciprocal beating is initiated by a premature beat of the atria, ventricles, or A-V node,⁷ but in the case recently presented by Eldridge⁸ a rhythmic sinoatrial pacemaker seemed to be responsible. We agree with Eldridge that the distinction between coupled atrial premature systoles and reciprocal beating is not easily made.

Retrograde (ventriculo-atrial) conduction, related to reciprocal beating, is illustrated in various situations by Figs. 6 through 8. Daniélopolu and Danulesco^{9,10} are thought to have been the first workers to suggest retrograde conduction as an explanation for inverted P waves occurring in standard leads during A-V block. Retrograde conduction in complete atrioventricular block is uncommon, but probably not rare, since Winternitz and Langendorf¹¹ reported a series of 25 cases compiled from their own records and from the literature. In addition, Kistin and Landowne,¹² reporting on the incidence of retrograde conduction to the atria from ventricular premature contractions, found this phenomenon in 15 of 33 unselected individuals studied with the unipolar esophageal lead. More recently, Bussan, Torin, and Scherf¹³ reported a similar study of 35 patients (also with ventricular premature contractions), using the esophageal electrode, and found that in 25 subjects a sinus tachycardia prevented the occurrence of retrograde conduction. Retrograde conduction was found, however, in 8 of 9 subjects with ventricular extrasystoles and a slow sinus rhythm.

Ventricular tachycardia with retrograde conduction has been reported a number of times¹⁴⁻¹⁶ since Scott's¹⁷ initial report in the early twenties. In 1950, Foster and Thayer¹⁸ reported a similar case which they studied with the esophageal lead technique, and also reviewed the literature on the subject. Of the 81 cases which they reviewed, approximately half failed to exhibit discernible atrial activity, 18 showed an independent atrial mechanism, 14 showed atrial fibrillation, and 9 exhibited retrograde conduction. Three cases out of this last

group seemed to show 1:1 retrograde conduction, whereas the remaining 6 showed partial block of the retrograde impulses. Our case (Fig. 8) falls into the latter category.

On taking the long view of this report, it can be said to constitute both a clinical trial of the bipolar esophageal electrode and a comparative study of the clinical utility of the bipolar esophageal lead, the unipolar esophageal lead, and the Einthoven lead in the diagnosis of cardiac arrhythmias. We have found the bipolar electrode to be superior in many instances. The previously voiced objection¹⁴ to the bipolar esophageal lead, i.e., that the cancellation of the ventricular complex may prove a disadvantage rather than an advantage, can usually be obviated by changing slightly the level of the esophageal electrode. It is, of course, ideal to have a simultaneous standard lead for reference, but our experience shows that in most situations encountered the paucity of information derived from the standard lead relevant to atrial activity serves to emphasize the usefulness of the bipolar esophageal lead.

SUMMARY

1. The application of the salt-bridge method of esophageal electrocardiographic registration to the development of a simple and clinically reliable bipolar esophageal lead has been outlined. The results of multichannel, multilevel esophageal lead surveys made with this device upon 26 subjects with normal sinus mechanism and 74 with various cardiac arrhythmias are reported here. The leads which were routinely recorded simultaneously in these surveys include unipolar registration from the proximal and distal members of the lead assembly (VE_P and VE_D), the difference in potential between these two members (Lead BE), and a conventional extremity lead (usually Lead II).

2. A careful and extensive analysis of the group of subjects with normal sinus rhythm confirms that both the unipolar and bipolar esophageal leads greatly exceed the capability of conventional body surface leads in depicting the forces of atrial depolarization and repolarization. In this group the bipolar esophageal leads appeared to have certain advantages as compared to the unipolar leads, and in no instance did they prove inferior to the unipolar leads.

3. In our evaluation of the group of subjects with cardiac arrhythmias the esophageal leads offered unsurpassable diagnostic superiority as compared to the conventional leads. In a number of cases the bipolar esophageal lead was decidedly better than the unipolar leads, although this was not invariably so.

4. Our clinical observations of the unipolar and bipolar esophageal electrocardiograms appear to confirm the theoretical principles which were previously developed in this laboratory. As anticipated, the bipolar lead has proved to be particularly sensitive to alterations in the time course of atrial depolarization. It also provides a ready means for sorting atrial from ventricular deflections, especially in situations in which they occur concomitantly.

5. On the basis of the experiences reported here, we believe that no complicated or perplexing arrhythmia will have been studied adequately without the benefit of esophageal tracings. The relative technical simplicity of the salt-

bridge principle as applied to unipolar and bipolar esophageal registration greatly minimizes the demands which such a procedure would ordinarily impose upon the physician's time and energy.

The authors are indebted to Dr. David S. Carroll for the roentgenographic service and interpretation employed in this study. Dr. John M. Barron participated in the initial phase of the study. Mr. Morris Frazier served as technician, and aided in preparation of the illustrations.

REFERENCES

1. Brody, D. A., Harris, T. R., and Romans, W. E.: AM. HEART J. **50**:923, 1955.
2. Brody, D. A., and Copeland, G. D.: AM. HEART J. **57**:3, 1959.
3. Copeland, G. D., Tullis, I. F., and Brody, D. A.: AM. HEART J. **57**:862, 1959.
4. Moe, G. K., Preston, J. B., and Burlington, H.: Circulation Res. **4**:357, 1956.
5. Scherf, D., and Shookhoff, C.: Arch. inn. Med. **10**:97, 1925. Cited by Winternitz and Langendorf.¹¹
6. Scherf, D., and Shookhoff, C.: Arch. inn. Med. **12**:501, 1926. Cited by Winternitz and Langendorf.¹¹
7. White, P. D.: Arch. Int. Med. **16**:517, 1915.
8. Eldridge, F. L.: AM. HEART J. **55**:469, 1958.
9. Daniélopolu, D., and Danulesco, V.: Bull. et mém. Soc. méd. hôp. de Bucarest **1**:7 and 20, 1919; and **3**:6, 1921. Cited by Winternitz and Langendorf.¹¹
10. Daniélopolu, D., and Danulesco, V.: Arch. mal. coeur **15**:365, 1922. Cited by Winternitz and Langendorf.¹¹
11. Winternitz, M., and Langendorf, R.: AM. HEART J. **27**:301, 1944.
12. Kistin, A. D., and Landowne, M.: Circulation **3**:738, 1951.
13. Bussan, R., Torin, S., and Scherf, D.: Am. J. M. Sc. **230**:293, 1955.
14. Kistin, A. D., and Bruce, J. C.: AM. HEART J. **53**:65, 1957.
15. Katz, L., and Pick, A.: Clinical Electrocardiography. Part I: The Arrhythmias, Philadelphia, 1956, Lea & Febiger.
16. Bellet, S.: Clinical Disorders of the Heart Beat, Philadelphia, 1953, Lea & Febiger.
17. Scott, R. W.: Heart **9**:297, 1921-22.
18. Foster, R. F., and Thayer, R. H.: AM. HEART J. **40**:224, 1950.

Acetyl Strophanthidin Sensitivity in Dogs With Congestive Heart Failure

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Serious cardiac arrhythmias due to digitalis preparations have been observed rarely in the normal human being except when many times the usual dose of the drug was taken with suicidal intent.¹⁻⁴ On the other hand, such arrhythmias are a well-known hazard of the use of digitalis in ordinary doses in patients with heart disease. This hazard, for unknown reasons, appears to be greater the more severe the heart disease.⁵⁻⁷ We are reporting similarly increased sensitivity for arrhythmias, in this case caused by acetyl strophanthidin, in dogs with experimental congestive heart failure.

Acetyl strophanthidin, an esterified aglycone of *Strophanthus kombe*, possesses inotropic properties in cardiac muscle similar to those of digitalis preparations.⁸ K-strophanthoside is also similar to these compounds in its action on ventricular excitability and impulse conduction through various cardiac tissues.⁹ Soloff¹⁰ reported that acetyl strophanthidin in normal human beings caused no arrhythmias in doses sufficient to produce serious cardiac toxicity in patients with heart disease. The drug therefore appears to be analogous to the digitalis glycosides, although it is more rapid in its action.

METHODS

The syndrome of congestive heart failure developed in mongrel dogs following the two-stage surgical production of tricuspid insufficiency and stenosis of the main pulmonary artery by a modification of the technique of Barger and co-workers.¹¹ If ascites, the major clinical manifestation of cardiac failure in these dogs, did not appear within 3 months of the second operation, the pulmonary artery was further narrowed at a third operation.

These and similar animals in our laboratory have demonstrated, besides ascites, elevated right atrial mean pressure and right ventricular systolic and end-diastolic pressure, subnormal cardiac output, severely congested liver, dilated and thickened right ventricle, and increased heart weight: ascites-free body weight ratio. Congestive heart failure, resembling that seen in human beings, was diagnosed on the basis of this evidence and of data reported by Davis and associates^{12,13} and Barger and co-workers¹¹ in similar animals.

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Fifteen normal dogs and 5 dogs with congestive heart failure were anesthetized with intravenous sodium pentobarbital, 25 mg. per kilogram. The duration of appreciable ascites in the latter animals is noted in Table I. The electrocardiogram (Lead II) was recorded on a Sanborn Viso-Cardiette immediately before the intravenous administration of acetyl strophanthidin,* and afterward for the first 10 to 15 seconds of each minute for 18 to 20 minutes. Acetyl strophanthidin was given in saline over a 2-minute period. Zero time was taken to occur at the middle of this period. In dogs with congestive failure, the ascites-free weight was estimated and a dose of 0.03 mg. per kilogram of ascites-free weight given on the basis of this estimate. The true ascites-free weight was determined at the time of sacrifice, an average of 9 days later. The dose of acetyl strophanthidin per kilogram of true ascites-free weight is noted in Table I. All normal dogs received 0.03 mg. per kilogram of body weight.

Samples of venous blood were drawn before and 8 minutes after the administration of acetyl strophanthidin. Concentration of serum potassium, noted in Tables I and II, was determined with a Perkin-Elmer internal standard flame photometer. The respiratory rate was noted each minute.

RESULTS

Four of the 5 dogs having congestive heart failure developed serious and prolonged toxicity following the administration of acetyl strophanthidin. The fifth animal showed no arrhythmia (Table I). Of 15 normal dogs receiving the same dose of the drug, none developed serious toxicity, although eight sporadic premature beats occurred in 2 animals during the procedure and were considered to be evidence of minor toxicity (Table II). The difference in incidence of major toxicity between the normal animals and those with congestive failure is statistically significant ($P < .01$) by chi-square adjusted for continuity.¹⁴

In dogs with congestive failure and serious toxicity (Figs. 1 and 2), the heart rate slowed immediately after administration of acetyl strophanthidin. This relative bradycardia persisted without change in P-R interval. Soon, definitely abnormal QRS complexes appeared. These were not only different in configuration but wider than the control QRS, ranging from 0.06 to 0.10 second in duration. P waves were always visible at this time, and the aberrantly conducted ventricular beats were premature, often occurring in a bigeminal relationship to normal QRS complexes.

The pacemaker originating the abnormal QRS complex then assumed control of the ventricles, usually at a slightly irregular rhythm, and always at a rate slightly faster than the sinus rate. Several forms of abnormal QRS complex, one form often alternating with a slightly wider form in a bigeminal relationship, the more abnormal QRS being slightly premature, were seen in each animal during the period of toxicity. P waves, with P-R interval less than control, occurred before each QRS complex early in the arrhythmia, but subsequently disappeared as the ventricular rate exceeded the atrial rate. On some occasions, regular P waves, at a rate slightly slower than that of the QRS complexes, recurred, only to disappear once more.

From time to time the arrhythmia was interrupted by a pause followed by a P wave giving rise to a normal QRS complex. After this event the arrhythmia resumed. In 2 animals the QRS duration reached 0.12 second, these complexes

*Acetyl strophanthidin was kindly supplied by Dr. B. L. Martz and Dr. G. C. Chiu, Eli Lilly & Company.

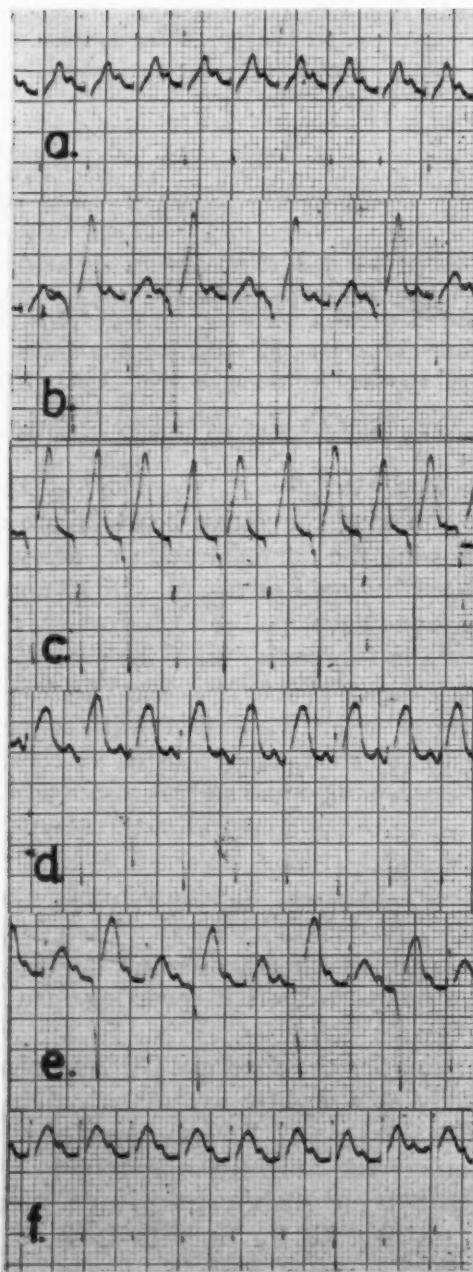


Fig. 1.—Dog 2. *Times* after acetyl strophanthidin noted. *a*, Control. Sinus rhythm, QRS 0.05 sec. duration. *b*, 1 minute. Bigeminy, premature QRS complexes, 0.08 sec. *c*, 2 minutes. Alternation between two types of QRS complex, 0.06 sec. and 0.08 sec.; no P waves seen. *d*, 11 minutes. P waves reappear; P-R 0.06 to 0.09 sec.; QRS abnormal, 0.055 sec. *e*, 17 minutes. Bigeminy, premature QRS complexes, 0.07 sec. *f*, 19 minutes. Sinus rhythm, QRS 0.05 sec.

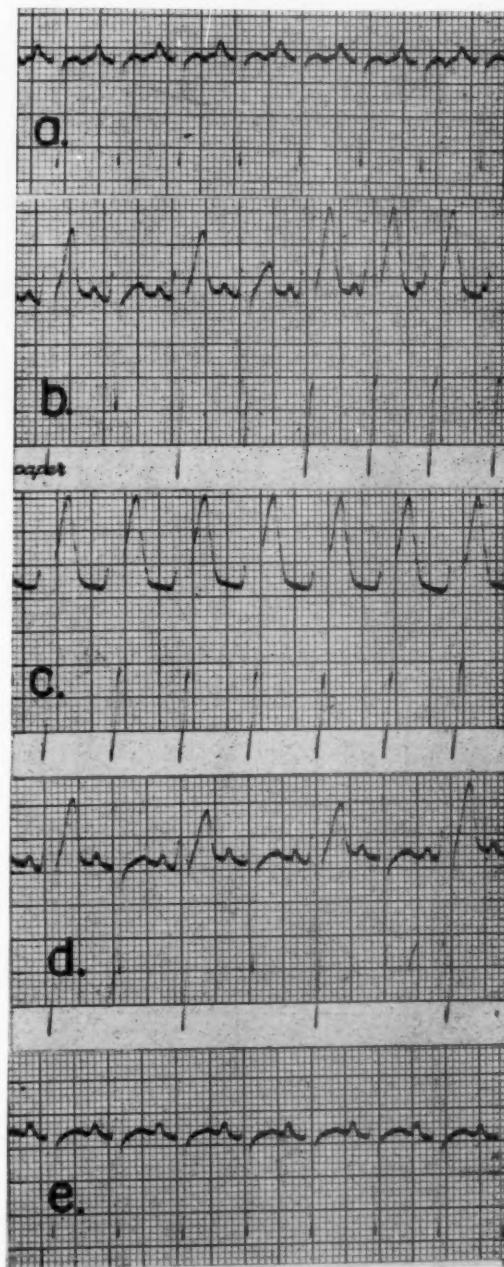


Fig. 2.—Dog 3. Times after acetyl strophanthidin noted. *a*, Control. Sinus rhythm, QRS 0.06 sec. duration. *b*, 4 minutes. Bigeminy, premature QRS, 0.09 to 0.10 sec.; preceding QRS is 0.08 sec. A-V dissociation occurs as pacemaker originating QRS of 0.12 sec. assumes control of ventricles at a rate slightly faster than sinus. *c*, 8 minutes. QRS 0.12 sec.; no P waves seen. *d*, 11 minutes. Bigeminy, premature QRS complexes, 0.09 sec. *e*, 16 minutes. Sinus rhythm. QRS 0.06 sec.

TABLE I. DOGS WITH CONGESTIVE HEART FAILURE

DOG	DOSE OF ACETYL STROPHANTHIDIN (MG./KG. TRUE ASCITES-FREE WEIGHT)	DAYS AFTER APPEAR-ANCE OF ASCITES	CONTROL		8 MINUTES SERUM K (mEq./L.)	CHANGE IN SERUM K (mEq./L.)	EVIDENCE FOR TOXICITY	ONSET OF TOXICITY (MINUTES AFTER DRUG)	OFFSET OF TOXICITY (MINUTES AFTER DRUG)
			RHYTHM	SERUM K (mEq./L.)					
1.	0.030	2	Sinus	3.96	4.12	+0.16	None	-	—
2.	0.029	5	Sinus	4.08	4.30	+0.24	A-V dissociation, abnormal QRS complexes	1	19
3.	0.034	20	Sinus	4.51	4.41	-0.10	A-V dissociation, abnormal QRS complexes	4	16
4.	0.027	246	Sinus	3.88	3.91	+0.03	A-V dissociation, abnormal QRS complexes	9	12
5.	0.025	298	Sinus	—	—	—	A-V dissociation, abnormal QRS complexes	3	20
Mean ± Standard Deviation	0.029 ± .003			4.11 ± .28	4.19 ± .22	+0.08 ± .15			

TABLE II. NORMAL Dogs

DOG	CONTROL		8 MINUTES		CHANGE IN SERUM K (mEq./L.)	EVIDENCE FOR TOXICITY (MINUTES AFTER DRUG)
	RHYTHM	SERUM K (mEq./L.)	SERUM K (mEq./L.)	SERUM K (mEq./L.)		
N-1.	Sinus	3.96	4.54	+0.58	None	
N-2.	Sinus	2.82	3.63	+0.81	None	
N-3.	Sinus	4.44	3.92	-0.52	None	
N-4.	Sinus arrhythmia	3.89	4.29	+0.40	None	
N-5.	Sinus	4.28	4.64	+0.36	None	
N-6.	Sinus arrhythmia	3.56	3.80	+0.24	None	
N-7.	Sinus	3.65			None	
N-8.	Sinus	3.50	4.05	+0.55	None	
N-9.	Sinus arrhythmia	3.89	4.82	+0.93	3 premature beats, 2 consecutive; QRS 0.06 to 0.09 sec., at 5 min. 3 premature beats; QRS 0.08 sec., at 18 min.	
N-10.	Sinus arrhythmia	4.58	4.51	-0.07	1 premature beat; QRS 0.07 sec., at 6 min. 1 premature beat; QRS 0.07 sec., at 7 min. 1 blocked sinus beat at 10 min.	
N-11.	Sinus	3.68	4.55	+0.87	None	
N-12.	Sinus	3.92	4.50	+0.58	None	
N-13.	Sinus	3.47	4.24	+0.77	None	
N-14.	Sinus	3.74	4.23	+0.49	None	
N-15.	Sinus	2.88	4.21	+1.33	None	
Mean		3.75	4.28	+0.52		
± Standard Deviation		± .49	± .34	± .45		

in one dog persisting as a regular rhythm for 5 minutes, and in the other occurring as isolated premature beats. The arrhythmia waned in reverse order of its appearance, with bigeminy occurring first, followed by regular sinus rhythm.

If the arrhythmia occurred very early after administration of the drug, it persisted longer than in the animals in which its appearance was somewhat delayed. The median time of arrhythmia averaged 10.5 minutes after acetyl strophanthidin (range, 10 to 11½ minutes).

In all normal animals and in one animal which had had demonstrable ascites for only 2 days, sinus rhythm persisted following acetyl strophanthidin, with the minor exceptions noted in Table II. Sinus slowing and T-wave changes usually associated with digitalis effect occurred after administration of the drug in these animals in at least the amount seen in dogs with congestive failure.

Mean control and 8-minute concentrations of serum potassium were not significantly different in the two groups of dogs. The normal dogs, however, showed by "t" test¹⁴ a significant rise ($P < .001$) in concentration of serum potassium after the administration of acetyl strophanthidin, while the animals with congestive heart failure showed an insignificant rise ($P > .3$). The two groups therefore differed significantly in concentration response of serum potassium to acetyl strophanthidin.

Respiratory rate in both groups of animals generally fell immediately after the administration of acetyl strophanthidin, reaching a minimum about 3 minutes later and recovering during the next few minutes. In 2 of the 4 animals showing serious arrhythmias, respirations had returned to normal when toxicity was at its peak.

DISCUSSION

In our animals with congestive heart failure, A-V dissociation appeared when a pacemaker in the A-V node or below developed a rate faster than that of the sinus node. This arrhythmia was always preceded by sinus slowing but in no instance by prolongation of the P-R interval. Bigeminy occurred before complete A-V dissociation. The pacemaker originating the premature beat in the bigeminal rhythm subsequently gained full control of the ventricles when A-V dissociation appeared. In each animal these ventricular complexes were different from those in the control in form and duration, the latter varying from 0.06 to 0.12 second.

It is possible that the pacemaker controlling the ventricles in this arrhythmia was located in the A-V node or bundle of His, and that its impulses were conducted with abnormal slowness to the ventricles, resulting in QRS prolongation. In this event, one might expect to see gradual prolongation of all QRS complexes before A-V dissociation began. Since this was not the case, however, it is more likely that the ventricular complexes originated either in ordinary myocardial cells, separated by various distances from the conduction network, or in ventricular Purkinje fibers variably distant from the bundle of His. With either possibility, slight reduction of Purkinje conduction velocity could materially add to the QRS prolongation caused by the abnormal location of the pacemaker.

Slight changes in location of the pacemaker could cause the variations in QRS form and duration seen in individual animals.

In human beings with heart disease similar arrhythmias may be seen. Bigeminy, of course, may follow the administration of digitalis. When A-V dissociation appears, normal QRS complexes may be present,¹⁵ but slight to profound QRS abnormalities occur in some patients, especially those with seriously damaged hearts.¹⁶⁻¹⁹ In clinical usage these arrhythmias are usually labeled as ventricular tachycardia or nodal tachycardia with aberrant intraventricular conduction. A-V dissociation is, of course, a requisite for their appearance. In some reported instances,¹⁵ after the appearance of bigeminy the pacemaker originating the ventricular premature beat intermittently captured complete control of the ventricles in a regular rhythm faster than that of the sinus node. In other patients,²⁰⁻²³ two pacemakers generating abnormal QRS complexes have alternated with each other during the period of A-V dissociation. These events resemble those in our animals with congestive heart failure.

At least two general mechanisms may be involved in the production of such arrhythmias in congestive heart failure by doses of acetyl strophanthidin that are nontoxic to normal individuals. First, more drug may be available to the heart in cardiac failure, and its action on body electrolyte equilibria may be different than in normal individuals. Second, the failing heart may possess increased sensitivity to digitalis because of factors unique to its myocardial cells or because of nervous, humoral, or other factors, peculiar to the congestive failure syndrome, operating on these cells.

The second mechanism has been invoked by most investigators.⁵⁻⁷ Some evidence may be adduced for the first, however. As Lown and his co-workers²⁴ have recently shown in normal dogs, about three times as much acetyl strophanthidin is needed to produce ventricular tachycardia when the drug is injected into the portal vein as when it is given into a systemic vein. This appears to indicate that the normal liver renders a large fraction of the administered drug incapable of producing cardiac arrhythmias. That the congested liver in cardiac failure may perform this function inadequately is suggested by the subnormal ability of the congested or hypoxic liver to metabolize aldosterone, cortisol, and other steroids.^{25,26} Digitalis and Strophanthus derivatives also have steroid nuclei.

Our normal animals experienced a greater rise in the concentration of serum potassium after acetyl strophanthidin than did the dogs with congestive failure. It is possible that this effect may have contributed to preventing cardiac toxicity in normal animals, in view of the undoubtedly therapeutic action of potassium salts in digitalis-induced arrhythmias.⁶ Lown and associates²⁴ demonstrated a greater increase in the concentration of serum potassium when acetyl strophanthidin was introduced into the portal circulation than when it was given into the systemic circulation. The congested liver, if incapable of metabolizing digitalis compounds normally, as suggested above, might therefore be partially responsible for the subnormal rise in the concentration of serum potassium.

During the last decade, studies of the electrophysiologic properties of heart muscle have shed new light on the possibility of increased myocardial sensitivity in congestive failure to ordinarily nontoxic doses of digitalis. Using *in situ* dog

hearts, Moe and Mendez⁹ showed that digitalis-like preparations probably did not slow conduction velocity in nonspecialized myocardial tissue but did so in Purkinje fibers. Swain and Weidner²⁷ corroborated this finding in the dog heart-lung preparation and observed that occasionally, just before ventricular fibrillation occurred, the Purkinje system no longer conducted impulses faster than the ordinary muscle fibers.

The sinus node and the Purkinje tissue of the A-V node and ventricles are unique in that the resting membrane potential of their cells decreases slowly to a threshold level at which rapid depolarization occurs.²⁸ In an isolated rabbit atrium preparation, West²⁹ demonstrated that the exact location of the pacemaker within the sinus node was determined by the rate of diastolic depolarization in individual cells in the node. The cells depolarizing fastest in diastole initiated the propagated disturbance which ultimately depolarized other cells of the sinus node as well as ordinary atrial muscle fibers. Corabœuf and co-workers³⁰ showed that digitoxin can increase the speed of slow diastolic depolarization in canine Purkinje tissue.

Decrease in rate of the sinus node, together with slowed conduction and increased rate of diastolic depolarization in Purkinje tissue following the administration of digitalis, favor establishment of a pacemaker in the A-V node or below. In normal human beings, however, as noted previously, huge doses of digitalis were needed to produce such pacemakers. Even in animals, in which anesthesia plays an unknown role, large doses of digitalis usually caused A-V block before an abnormal pacemaker took control of the ventricles.³¹ Kobacker and Scherf³² found that only after damaging one or both branches of the bundle of His would ordinary doses of digitalis produce a stable idioventricular pacemaker.

Therefore, despite the possibility, noted above, that a larger than normal fraction of administered digitalis may be available to the heart in congestive failure, it is appropriate to examine the action of factors, unique to the damaged heart, which may act concertively with digitalis to establish ventricular pacemakers.

Because of elevated diastolic filling pressure and subnormal ejection of blood, failing hearts are more than normally stretched. Dudel and Trautwein³³ showed that stretch produced rapid diastolic depolarization and local pacemaker formation in dog Purkinje fibers. Stretch and local pressure have been shown to cause increased rhythmicity in dog auricle³⁴ and frog sartorius.³⁵ Stretch would also be expected to decrease conduction velocity in Purkinje tissue by decreasing fiber diameter.³⁶ If high concentrations of epinephrine are present in failing cardiac muscle, as indicated by Raab and Gigee,³⁷ this influence might also be expected to increase the rate of diastolic depolarization in Purkinje fibers.³⁸

In canine Purkinje fibers, anoxia has been shown to decrease conduction velocity, to speed diastolic depolarization, and to cause the appearance of new pacemakers.³⁹ Fatigued isolated Purkinje fibers show faster diastolic depolarization than normal.⁴⁰ Sodium cyanide and other agents blocking cell respiration may also produce more rapid diastolic depolarization.²⁸ The importance of such factors as these for failing heart muscle in the intact animal is conjectural. The

rate of diastolic depolarization depends in part, however, on the adequacy of the sodium-pump mechanism for preventing sodium from entering the cell. This, in turn, depends upon oxidative metabolism and the availability of adenosine triphosphate, which may be subnormal, at least in some types of cardiac failure.⁴¹

These influences, by slowing the sinus node, by diminishing conduction velocity, and by increasing the rate of slow diastolic depolarization in the A-V node and Purkinje network, or by creating slow diastolic depolarization in ordinary ventricular muscle fibers, increase the likelihood of establishing a ventricular pacemaker in Purkinje tissue or in the myocardium itself. In diseased hearts such factors may add to the effect of digitalis to produce this end.

Therefore, the state of both the liver and the myocardium may be important in explaining the low incidence of digitalis arrhythmias in normal animals and human beings, and the greater frequency of these events in congestive heart failure.

SUMMARY

Fifteen normal dogs and five dogs with experimental congestive heart failure were given standard doses of acetyl strophanthidin on the basis of ascites-free weight. Four animals with cardiac failure developed persistent atrioventricular dissociation with abnormal QRS complexes, whereas no normal dog showed a serious arrhythmia. The normal dogs demonstrated a greater rise in the concentration of serum potassium after acetyl strophanthidin than did the animals with congestive failure.

Analysis of the electrocardiograms suggests that atrioventricular dissociation may occur as a result of simultaneous slowing of the sinus node, slowed conduction velocity in intraventricular conduction tissue, and increased rhythmicity of one or more foci in this tissue or in ordinary myocardial fibers.

The available evidence suggests that physical, nervous, and chemical factors operating on the failing heart could explain its increased sensitivity to digitalis-like compounds. It is also possible that the congested liver makes a larger fraction of administered drug available to the heart and is incapable of producing the normal rise in the concentration of serum potassium after digitalis has been administered.

REFERENCES

1. McGuire, J., and Richards, C. E.: *AM. HEART J.* **12**:109, 1936.
2. Bickel, G., Plattner, H., and Edelstein, H.: *Arch. mal. coeur* **44**:61, 1951.
3. Liljestrand, A.: *Cardiologia* **15**:357, 1949-50.
4. Bergy, G. G., Fergus, E. B., and Bruce, R. A.: *Ann. Int. Med.* **46**:964, 1957.
5. Sagall, E. L., and Wolf, L.: *New England J. Med.* **240**:676, 1949.
6. Lown, B., and Levine, S. A.: *Current Concepts in Digitalis Therapy*, Boston, 1954, Little, Brown & Co.
7. Craig, L. C., Lown, B., and Levine, S. A.: *J.A.M.A.* **166**:2139, 1958.
8. Greiner, T., and Reilly, J.: *Proc. Soc. Exper. Biol. & Med.* **81**:141, 1952.
9. Moe, G. K., and Mendez, R.: *Circulation* **4**:729, 1951.
10. Soloff, L. A., Zatuchni, J., and Velasquez, J.: *New England J. Med.* **254**:733, 1956.
11. Barger, A. C., Roe, B. B., and Richardson, G. S.: *Am. J. Physiol.* **169**:384, 1952.
12. Davis, J. O., Howell, D. S., and Hyatt, R. E.: *Circulation Res.* **3**:259, 1955.

13. Davis, J. O., Goodkind, M. J., Pechet, M. M., and Ball, W. C.: Am. J. Physiol. **187**:45 1956.
14. Snedecor, G. W.: Statistical Methods, Ames, Iowa, 1956, Iowa State College Press.
15. Katz, L. N., and Pick, A.: Clinical Electrocardiography, Part I: The Arrhythmias, Philadelphia, 1956, Lea & Febiger.
16. Moll, A.: Ärztl. Forsch. **7**:137, 1953.
17. Reid, W. D.: Arch. Int. Med. **33**:23, 1924.
18. Stellar, L. I.: Ann. Int. Med. **32**:717, 1950.
19. Levine, H. D.: Ann. Int. Med. **29**:822, 1948.
20. Smith, W. C., and Tenn, N.: AM. HEART J. **3**:723, 1927-28.
21. Wilkinson, K. D.: Brit. Heart J. **4**:1, 1942.
22. Palmer, R. S., and White, P. D.: AM. HEART J. **3**:454, 1927-28.
23. Schwensen, C.: Heart **9**:199, 1921-22.
24. Lown, B., Whipple, G. H., Shoemaker, W. C., Craig, L. C., and Levine, S. A.: Circulation **18**:753, 1958.
25. Yates, F. E., Urquhart, J., and Herbst, A. L.: Am. J. Physiol. **194**:65, 1958.
26. Chart, V. V., Gordon, E. S., Helmer, P., and Lesner, M.: J. Clin. Invest. **35**:254, 1956.
27. Swain, H. H., and Weidner, C. L.: J. Pharmacol. & Exper. Therap. **120**:137, 1957.
28. Weidmann, S.: Elektrophysiologie der Herzmuskelfaser, Bern, 1956, H. Huber.
29. West, T. C.: J. Pharmacol. & Exper. Therap. **115**:283, 1955.
30. Corabœuf, E., Loze, C., and Boistel, J.: Comptes Rendus Soc. Biol. **147**:1169, 1953.
31. Robinson, G. C., and Wilson, F.: J. Pharmacol. & Exper. Therap. **10**:491, 1917-18.
32. Kobacker, J. L., and Scherf, D.: Ztschr. ges. exper. Med. **67**:372, 1929.
33. Dudel, J., and Trautwein, W.: Cardiologia **25**:344, 1954.
34. Scherf, D., Scharf, M. D., and Goklen, M. F.: Proc. Soc. Exper. Biol. & Med. **70**:708, 1949.
35. Adrian, E. D., and Gelfan, S.: J. Physiol. **78**:271, 1933.
36. Hodgkin, A. L.: J. Physiol. **125**:221, 1954.
37. Raab, W., and Gigea, W.: Circulation **11**:593, 1955.
38. Cranefield, P. F., and Hoffman, B. F.: Physiol. Rev. **38**:41, 1958.
39. Trautwein, W., Gottstein, U., and Dudel, J.: Pflüger's Arch. ges. Physiol. **260**:40, 1954.
40. Draper, M. H., and Weidmann, S.: J. Physiol. **115**:74, 1951.
41. Hochrein, H., Doring, H. J., Drom, R., and Knopp, A.: Pflüger's Arch. ges. Physiol. **267**:313, 1958.

The Effect of Ganglionic Blockade on Venous Pressure and Blood Volume: Further Evidence in Favor of Increased Venomotor Tone in Congestive Heart Failure

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In the genesis of the syndrome of congestive heart failure it has long been considered that increased venous pressure follows as a consequence of increased blood volume. The observations that blood volume is not increased in some patients in failure,¹ and that a prompt drop in venous pressure is produced by ganglionic blockade² have cast doubt on the "classical" concept of hypervolemia as the determinant of venous hypertension. As an alternate hypothesis it has been suggested that the increased venous pressure is due to an increased venomotor tone.³ These two seemingly different explanations are not mutually exclusive if procedures purporting to reduce venomotor tone lower venous pressure by actually lowering circulating blood volume. The purpose of this study was to investigate the role that changes in circulating blood volume might play in the intermediate mechanism of action of ganglionic blockade on venous pressure.

METHODS AND MATERIALS

Forty patients from the wards of the Philadelphia General Hospital, Blockley Division, were studied. Twenty patients were in severe or moderately severe congestive heart failure, as characterized by dyspnea, orthopnea, pulmonary râles, markedly engorged jugular veins, hepatomegaly, and marked edema. A number of patients also had ascites. For the most part, the etiology of the heart disease was either arteriosclerotic or combined hypertensive and arteriosclerotic, while in a few cases it was rheumatic. Patients with cor pulmonale, anemia, or thiamin deficiency were avoided for reasons that will be discussed below. Twenty patients who served as controls were without heart disease. For the most part, they were convalescing from a variety of minor medical illnesses or were patients awaiting disposition. In a few, heart disease could not be completely ruled out. However, no one of this group was or had ever been in congestive failure to the best of our knowledge.

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The patients were brought to the laboratory and allowed to rest quietly for one hour. At the end of this time an indwelling needle was placed in an antecubital vein and a slow drip of 5 per cent dextrose in water was started. By means of a three-way stopcock, connection was made to a Statham strain gauge for the measurement of venous pressure. The zero level for the venous pressure was taken at the mid-chest level. A blood pressure cuff was placed on the upper arm on the contralateral side, and an indwelling styletted needle was placed in an antecubital vein in this arm. All injections were made through the tubing of the intravenous drip near the needle, and all samples were withdrawn from the styletted needle. Several readings of blood pressure, pulse rate, and venous pressure were made. When the values were found to be stable, a hematocrit was drawn and approximately 15 microcuries of radioactive iodinated human serum albumin with extra carrier pooled human serum albumin were injected.⁴ Samples for the calculation of the blood volume were drawn at 10, 15, and 20 minutes after injection of the isotope. Ten of the normal patients and 10 patients with congestive heart failure were then given 50 mg. of hexamethonium intravenously. The drug was diluted to 2.5 mg./ml. and administered to the patients at a rate of 1 ml. per minute for 20 minutes. The remaining individuals received an equal volume of 5 per cent dextrose in water. A second hematocrit was drawn, and calculation of the blood volume was then repeated in the manner described above, using approximately 90 microcuries of radioactive iodinated human serum albumin. Arterial pressure, pulse rate, and venous pressure were measured at frequent intervals throughout the procedure.

In the handling of the isotope the stock solution was diluted to the approximate strength and then drawn up into a 10-ml. syringe. The total counts injected were determined by measuring the counts per milliliter of an aliquot of the material injected and the weight of the injected solution. Calculation of the volume delivered from the syringe was considered to be too inaccurate. The isotope was delivered by puncturing the tubing of the intravenous drip near the needle and then flushing the tubing. If the isotope was lost during needle puncture of the tubing, the procedure was discontinued and the data for that case discarded. Injection of the material and withdrawal of samples were done at a uniform rate and were timed at the midpoint to the nearest minute. Ten-milliliter samples were drawn in syringes wetted with heparin and centrifuged at 2,500 r.p.m. for 10 minutes. Aliquots of the plasma were counted in a well-type scintillation counter. The blood volume was calculated from the plasma volume and the hematocrit. The observed hematocrit, centrifuged in the standard manner and read to the nearest 0.1 per cent, was corrected to "body hematocrit" by using the most recently available figure of 0.927.⁵ For the second blood volume the counts remaining in the blood drawn just prior to the injection of the second dose of isotope were subtracted from the counts obtained in the subsequent samples.

RESULTS

Fig. 1 shows the effect of hexamethonium on the blood pressure, pulse rate, and venous pressure of a patient without heart disease. Note the sharp and persistent drop in blood pressure with little or no change in either pulse rate or venous pressure. Fig. 2 shows the effects of hexamethonium on one of the patients in congestive heart failure. Again, note the sharp and persistent drop in blood pressure. There is a transient increase in pulse rate. The venous pressure, which is markedly elevated prior to the ganglionic blockade, drops precipitously and remains at low levels throughout the duration of the procedure. In most cases the venous pressure fell to normal levels. In all cases the drop was pronounced and stayed well below control levels for the duration of the procedure. All patients not given hexamethonium showed no significant change in blood pressure, pulse rate, or venous pressure.

In Fig. 3 a comparison is made of the blood volumes before and after either hexamethonium or the 5 per cent dextrose. In no instance can a significant change be observed. This figure shows the data on the plasma volume and

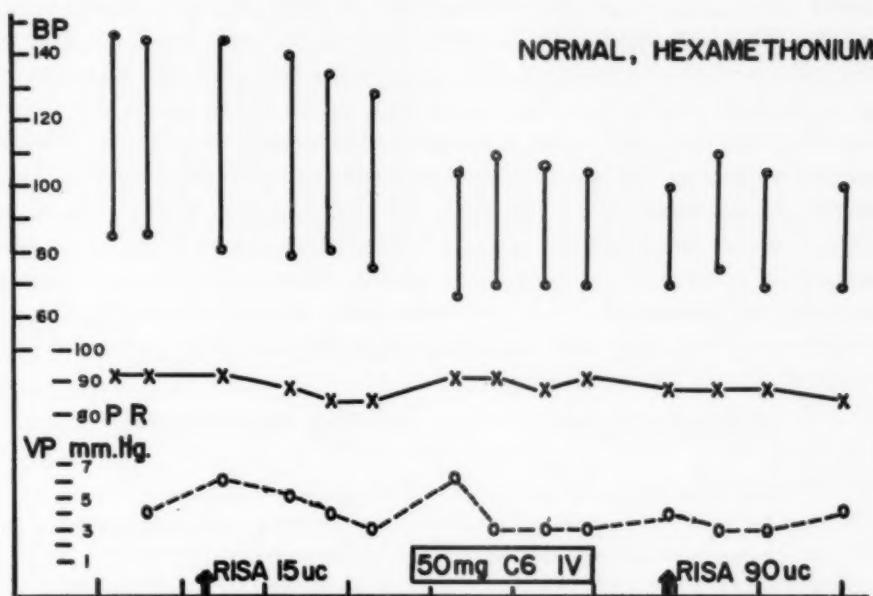


Fig. 1.—Blood pressure (BP), pulse rate (PR), and venous pressure (VP) in a normal patient given 50 mg. of hexamethonium intravenously. Blood volume determinations at the arrows. Description in the text.

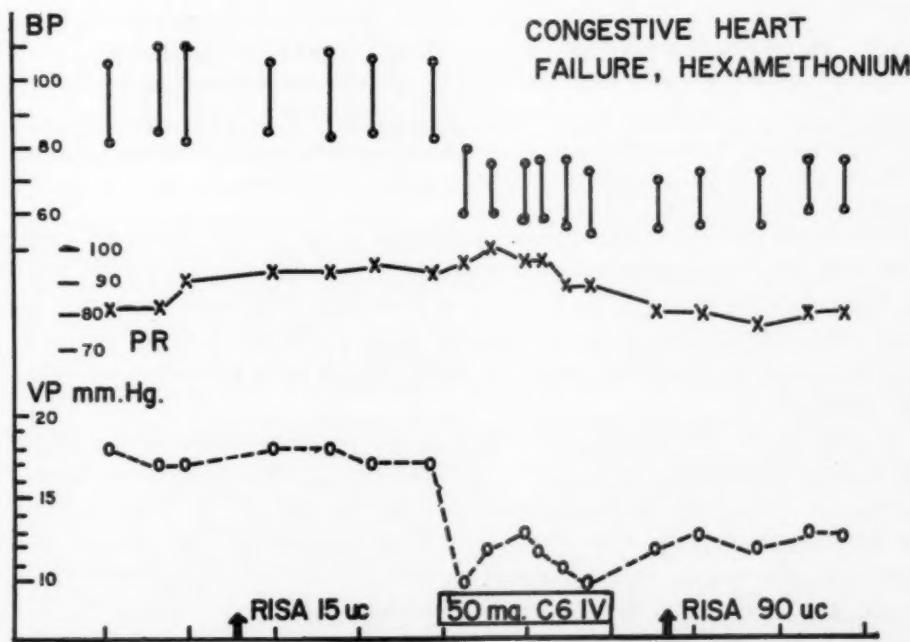


Fig. 2.—Blood pressure (BP), pulse rate (PR), and venous pressure (VP) in a patient in congestive heart failure given 50 mg. of hexamethonium intravenously. Blood volume determinations at the arrows. Description in the text.

hematocrit as measured, and for the red cell volume and total blood volume as calculated. The left-hand side of each box records the data for the normal patients (*N*), and the right-hand side records the data for the patients in congestive heart failure (*CHF*). The upper row shows those given the 5 per cent dextrose (*D*), and the lower row, those given hexamethonium (*C₆*). The figures in each cell represent the mean value and one standard deviation. For each patient the given value was calculated by dividing the second blood volume (determined after the administration of hexamethonium or 5 per cent dextrose) by the first blood volume. Comparison of any given cell with any other within the same box reveals no *P* value less than 0.02. Almost all of the *P* values lie above the level of 0.1. On this basis no comparison has been considered to show a statistically significant difference.

<u>PLASMA VOLUME</u>		<u>RED CELL VOLUME</u>			
	<u>N</u>	<u>CHF</u>			
D	1.03 ± .01	1.01 ± .03	D	0.98 ± .03	0.97 ± .03
	1.03 ± .03	1.05 ± .04		0.98 ± .02	0.98 ± .02
<u>TOTAL BLOOD VOLUME</u>		<u>HEMATOCRIT</u>			
	<u>N</u>	<u>CHF</u>		<u>N</u>	<u>CHF</u>
D	1.01 ± .02	0.99 ± .03	D	0.97 ± .02	0.98 ± .01
	1.01 ± .03	1.02 ± .04		0.97 ± .01	0.96 ± .02

Fig. 3.—Ratio of second blood volume to first blood volume. *N*, Normal. *CHF*, Congestive heart failure. *D*, 5 per cent dextrose infusion. *C₆*, 50 mg. hexamethonium intravenously. Description in the text.

Since the critical feature of our argument rests on the effect of ganglionic blockade on the blood volume and not on the absolute values, we have not tabulated these figures here. This point has been well discussed by other investigators. Our observations, in agreement with previous studies, indicate that most, but not all, patients in congestive heart failure have an increased circulating blood volume.*

Of interest is the observation that in all patients there was a slight but definite drop in hematocrit (range, 1 to 7 per cent). No hematocrit rose during the test. It may well be that this is due to the volume of administered fluid or to the change in posture of the patient from upright (or the patient being up and around the ward) to recumbent in the laboratory. It should be noted, however, that this drop in hematocrit correlates not with a suspected increase in measured plasma volume but rather with a decline in calculated red cell volume. On the other hand, recent observations in our laboratory concerned in

*For those interested, these tables are available from the authors upon request.

part with this point, in which red cell volume was measured using Cr⁵¹-tagged red cells in a smaller but comparable series of patients, fail to bear this out. For the present this observation remains unexplained.

DISCUSSION

These results indicate that in patients in congestive heart failure, ganglionic blockade (hexamethonium) lowers the venous pressure but does not significantly alter the circulating blood volume. Ganglionic blockade certainly does not decrease the circulating blood volume. If anything, there is a slight increase, but comparison with normal patients given hexamethonium and with patients in failure not given hexamethonium indicates that this rise is not outside the experimental error.

Repeated observations by other workers have demonstrated the lowering effect on venous pressure of ganglionic blocking agents. This effect has been interpreted as being due to a decrease in venomotor tone, without investigation of the question of alterations in circulating blood volume. Recent studies have investigated the effect of ganglionic blockade on circulating blood volume.⁶ The technique used has been that of observing the slope of the isotope disappearance from the blood following a single injection, and noting any change in that slope following administration of the test substance. This method will detect changes in blood volume in only one direction, however. Moreover, the direction that it notes is not the critical one for answering the question concerning the possible intermediate action of ganglionic blockade. In the situation in which ganglionic blockade were to cause fluid to be added to the circulating blood volume, this added volume, obviously untagged, would dilute the pre-existing volume and change the slope of the isotope disappearance curve. However, should the ganglionic blocking agent remove from the circulation a volume of previously tagged blood (the critical question to be answered), the disappearance curve, dependent on the concentration of the isotope remaining in the circulation, need not be altered. For this reason, the technique used in this study relied upon a second injection of isotope to measure the circulating blood volume after the administration of the test substance.

Since, by the test of ganglionic blockade, venous pressure and circulating blood volume act independently, it cannot be said that the level of venous pressure is set by the amount of circulating blood volume. On this basis then it is more realistic to regard the level of venomotor tone (the outpouring of impulses from the central nervous system) as the determinant of the level of venous pressure. The evidence from the rapidly growing literature on the problem of venous circulatory regulation would indicate that a simple mechanical explanation of venous return is inadequate.⁷ The studies of Gollwitzer-Meyer⁸ showed that the venules are supplied with nerve twigs in much the same way that the arterioles are. Studies in animals, in which one of us (D.H.L.) participated, revealed that vasomotor activity is not restricted to changes in arteriolar tone. Rather there is simultaneous and coordinated arteriomotor and venomotor activity.⁹ Studies of the forearm veins in human beings indicate important venomotor activity.¹⁰

In the genesis of venous hypertension seen in congestive heart failure there has been disagreement as to whether this is due to "backward" or "forward" failure. Proponents of "backward" failure see the reduction in myocardial contractility as the cause of a damming up of blood in the venous reservoir, while proponents of "forward" failure view the reduction in renal flow as initiating fluid retention, with consequent hypervolemia and venous hypertension. Both groups offer a mechanical explanation for venous hypertension. We would propose, instead, that the decrease in myocardial contractility produces a relative deficiency in the supply of blood to the tissues. This, in turn, initiates a reflex which calls into play increases in arteriomotor and venomotor tone. In this respect, the information supplied to the central nervous system by the tissues is similar to that seen in hemorrhage and in shock. In these cases this reflex acts in a compensatory manner. In myocardial disease this mechanism again would presumably act in a compensatory manner up to a certain point, beyond which it would be expected to add to the burden on the heart. One might further consider that when the embarrassment of the circulation to the tissues is caused by other than myocardial factors (e.g., pericardial constriction, etc.), venous hypertension might here be completely compensatory by adding a priming factor to the myocardium. In *cor pulmonale* the situation is somewhat more complicated, but the observation that ganglionic blockade produces peripheral vascular collapse in this condition agrees with this hypothesis, and seems, to us, to offer a more rational explanation than that the cause lies in the pulmonary vasculature.¹¹ For these reasons we have not studied the effects of ganglionic blockade in these types of congestive heart failure.

One criticism of the conclusions reached here would be that while the total circulating blood volume remains unchanged, the distribution of this volume within the vascular bed might change. In such a case the blood might leave the veins, lowering the venous pressure, and go to some other part of the circulation. The question is, to what other part. It has obviously not gone out of the pool of blood called "total circulating blood volume," since the technique used measures this parameter. It is therefore not cut off from the general circulation. The observation of Werkö and his co-workers¹² indicates that ganglionic blockade in congestive heart failure decreases the central blood volume. This hypothetical redistribution is therefore not in the central volume. One might consider that there has been a transfer of blood from veins to arteries. In the face of an absence of change in arterial distensibility a drop in arterial blood pressure, as seen in these experiments, might well indicate a decrease in arterial volume, certainly not an increase. Since our argument implies an increase in venous distensibility with ganglionic blockade, we cannot rule out an increase in arterial distensibility. Were arterial distensibility increased, the arterial volume might increase in the face of a declining arterial pressure. It seems likely, however, that such volume changes, if they occur, would be small. Furthermore, the technique of "central blood volume" measurement, in effect, includes much of the arterial system and, as previously noted, this volume decreases with ganglionic blockade. On the basis of volume alone, even though the arterioles are dilated, it would not appear that a significant volume could

be shifted to the arterioles. It could be in the capillaries. Again, on the basis of volume, this appears unlikely, but this point is far from clear. Until a suitable method for the measurement of systemic capillary blood volume becomes available, this question must remain unanswered.

SUMMARY

1. The effect of ganglionic blockade on venous pressure and on circulating blood volume was studied in 40 patients.
2. Twenty patients were normal and 20 were in congestive heart failure. Half of each group was given hexamethonium and the other half not.
3. In congestive heart failure, ganglionic blockade is associated with a drop in venous pressure, with no change in circulating blood volume.
4. Venous pressure in congestive heart failure is not strictly dependent on the level of circulating blood volume.
5. This is interpreted as further evidence in favor of increased venomotor tone as the important factor in the genesis of venous hypertension in congestive heart failure.

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REFERENCES

- 1a. Burch, G. E., and Ray, C. T.: *AM. HEART J.* **41**:918, 1951.
- 1b. Ross, J. F., Chodos, R. B., Baker, W. H., and Freis, E. D.: *Tr. A. Am. Physicians* **65**:75, 1952.
- 1c. Eisenberg, S.: *Circulation* **10**:902, 1954.
- 1d. Gunton, R. W., and Paul, W.: *J. Clin. Invest.* **34**:879, 1955.
- 2a. Relman, A. S., and Epstein, F. H.: *Proc. Soc. Exper. Biol. & Med.* **70**:11, 1949.
- 2b. Kelly, R. T., Freis, E. D., and Higgins, T. F.: *Circulation* **7**:169, 1953.
- 2c. Freis, E. D., Rose, J. C., Partenope, E. A., Higgins, T. F., Kelly, R. T., Schnaper, H. W., and Johnson, R. L.: *J. Clin. Invest.* **32**:1285, 1953.
- 2d. Burch, R. R.: *Circulation* **11**:271, 1955.
- 3a. Burch, G. E.: *Arch. Int. Med.* **94**:724, 1954.
- 3b. Burch, G. E.: *Arch. Int. Med.* **98**:750, 1956.
4. Beierwaltes, W. H., Johnson, P. C., and Solari, A. J.: *Clinical Use of Radioisotopes*, Philadelphia, 1957, W. B. Saunders Company, p. 198.
5. Beierwaltes, W. H., Johnson, P. C., and Solari, A. J.: *Clinical Use of Radioisotopes*, Philadelphia, 1957, W. B. Saunders Company, p. 196.
- 6a. Remenchik, A. P., and Moorhouse, J. A.: *Arch. Int. Med.* **100**:445, 1957.
- 6b. Samet, P., Fritts, H. W., Jr., Fishman, A. P., and Cournand, A.: *Medicine* **36**:211, 1957.
- 7a. Halmagyi, D., Felkai, B., Ivanyi, J., and Hetenyi, J., Jr.: *Brit. Heart J.* **14**:101, 1952.
- 7b. Freis, E. D., and Rose, J. C.: *Am. J. Med.* **22**:175, 1957.
8. Gollwitzer-Meier, K.: *Ergebn. Physiol.* **34**:1145, 1932.
9. Rashkind, W. J., Lewis, D. H., Henderson, J. B., Heiman, D. F., and Dietrick, R. B.: *Am. J. Physiol.* **175**:415, 1953.
- 10a. Duggan, J. J., Love, V. L., and Lyons, R. H.: *Circulation* **7**:869, 1953.
- 10b. Burch, G. E., and Murtadha, M.: *AM. HEART J.* **51**:807, 1956.
- 10c. Wood, J. E., Litter, J., and Wilkins, R. W.: *Circulation* **13**:524, 1956.
11. Sanctetta, S. M.: *AM. HEART J.* **49**:501, 1955.
12. Werkö, L., Frisk, A. R., Wade, G., and Eliasch, H.: *Lancet* **2**:470, 1951.

Kinetocardiographic Tracings as an Aid in the Differentiation of Three-Sound Rhythms

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INTRODUCTION

The differentiation between the ventricular gallop of mitral insufficiency and the opening snap of mitral stenosis is of practical importance. Such separation is usually based on the time of onset of these third heart sounds in relation to the second heart sound. A correlation of these and other third heart sounds with the onset of ventricular filling, as shown by the kinetocardiogram,¹ is believed to be a more accurate method of identification. The present report deals with the results of such a correlation.

METHODS

Standard phonocardiograms and kinetocardiograms were taken on 36 subjects, including patients with mitral stenosis, mitral insufficiency, and congestive heart failure without evidence of valvular lesions, as well as subjects who demonstrated split second sounds, and normal subjects. The electrocardiogram was used as a base line for timing purposes. The phonocardiograms were taken from the aortic and pulmonic areas, from the mid-precordium, and from the region of the apex.² They were recorded on the twin-beam Cambridge apparatus. The method for taking kinetocardiograms, which are recordings of low-frequency precordial movements at positions corresponding to the V-lead areas of the electrocardiogram, has been described previously.³⁻⁵ In several subjects the phonocardiogram and kinetocardiogram were taken on the same tracing, allowing for direct comparison between mechanical events. In others they were taken consecutively, mainly because of the poor response obtained from heart sound vibrations with direct-writing apparatus.

RESULTS

Tracings were taken on 10 patients who were found to have only mitral stenosis at subsequent valvulotomy. All of these patients showed a third sound occurring in early diastole on the phonocardiogram, and a well-defined early diastolic filling wave on the kinetocardiogram. The time interval between the onset of Q in the electrocardiogram was compared with the interval between Q and the onset of the filling wave in the kinetocardiogram. These time intervals

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were found to be consistently similar in all 10 patients, showing the simultaneous occurrence of the opening snap and onset of early ventricular filling.⁶ The following case history illustrates these findings.

Case History.—G.B.R., a white male contractor, 39 years of age, was admitted to the University Hospital in January, 1958. There was no history of acute rheumatic fever, but he had been rejected for military service in 1940, because of a heart murmur. He remained asymptomatic until 1951, when increasing exertional dyspnea, pedal edema, and palpitation forced him to seek medical advice. Auricular fibrillation developed in 1954. During the three years prior to admission he experienced three attacks of transient left-sided hemiparesis and aphasia, with some blurring of vision and memory impairment. Because these episodes were thought to be embolic phenomena, he was placed on anticoagulants.

Admission physical examination revealed a well-developed, well-nourished white man with a blood pressure of 140/85 mm. Hg; the pulse rate was 80 and irregular. A diffuse precordial systolic heave was noted. An early diastolic third sound and a diastolic rumble were heard at the apex. Venous pressure was 110 mm. Hg; arm-to-lung circulation time was 10 seconds, and arm-to-tongue was 20 seconds. The electrocardiographic and fluoroscopic findings indicated right ventricular enlargement. Tracings taken before operation showed that the third heart sound occurred at 0.08 second after the second heart sound and 0.48 second after Q, while the interval from Q to the beginning of filling time on the kinetocardiograms was 0.47 second. Thus, the third heart sound occurred at the onset of ventricular filling (Fig. 1). No systolic murmurs were found, and it was thought preoperatively that the patient had "pure" mitral stenosis. At operation a stenotic mitral valve without regurgitant jet was found. The postoperative course was uneventful.

A review of the records taken on the series of 10 similar subjects with uncomplicated mitral stenosis yielded results similar to those obtained on the patient cited above (Table I). The opening snap coincided exactly with the onset of ventricular filling in three instances, and in no subject did the two events differ by more than 0.02 second. The average difference was 0.009 second.

TABLE I

NUMBER OF SUBJECTS	Q-S ₁	Q-S ₂	Q-S ₃	S ₂ -S ₃	Q-CIN	Q-ONSET FILLING	FILLING TO S ₃	SUBJECT	GROUP
8	Mean	0.04	0.37	0.54	0.16	0.39	0.49	0.05	Normal
	Range	0.01	0.09	0.10	0.04	0.05	0.11	0.02	
9	Mean	0.04	0.36	0.53	0.17	0.40	0.46	0.07	Mitral Insufficiency
	Range	0.02	0.06	0.09	0.03	0.08	0.08	0.04	
3	Mean	0.04	0.35	0.49	0.15	0.36	0.43	0.07	Congestive Heart Failure
	Range	0.01	0.03	0.04	0.02	0.05	0.05	0.03	
10	Mean	0.07	0.36	0.46	0.10	0.39	0.46	0.009	Mitral Stenosis
	Range	0.04	0.12	0.11	0.06	0.09	0.10	0.02	
6	Mean	0.06	0.36	0.41	0.04	0.39	0.47	-0.06	Split Second Seconds
	Range	0.03	0.04	0.05	0.02	0.04	0.03	0.03	

Time intervals in hundredths of a second.

Similar tracings were taken on a series of 9 patients with the diagnosis of mitral insufficiency only. In confirmation of some of the findings of Contro,⁷ and other work as reported by Wood,⁸ all patients showed a third sound occurring in early diastole. Comparison of the time intervals between the Q wave of the electrocardiogram and the third sound in diastole and the interval between Q and the onset of filling showed that these third sounds fell after the onset of ventricular filling (Fig. 2; Table I). The average difference between the ventricular gallop and the onset of filling was 0.07 second.

Records were taken on 3 patients in untreated congestive heart failure who did not have evidence of concurrent valvular disease. Each of these patients had an early diastolic gallop. Comparison of time intervals revealed that the diastolic sound occurred 0.07 second after the onset of filling (Fig. 3; Table I). One of these subjects demonstrated a summation gallop, and the kinetocardiogram revealed that there was also summation of early diastolic and late diastolic (atrial) ventricular filling waves (Fig. 4).

Records were taken on 8 subjects with no history or physical findings of cardiac disease, in whom a third sound was audible. The third sound fell on an average of 0.05 second after the onset of early diastolic ventricular filling (Fig. 5; Table I). An atrial sound was also present in the records of one of those subjects (Fig. 6).

Six subjects with split second sounds were studied. The interval between the two components was on an average of 0.05 second, and the last component fell 0.06 second before the onset of ventricular filling (Fig. 7; Table I).

DISCUSSION

The results obtained from comparing the time of occurrence of third heart sounds and the onset of ventricular filling have shown that subjects may be classified broadly into three groups (Table I). The first group is one in which the third sound falls after the beginning of ventricular filling, and includes those patients with mitral insufficiency, those with congestive failure, and normal subjects who demonstrate physiologic third heart sounds. A second group, in which the third sound occurs with the onset of filling, is composed of patients with mitral stenosis. The third group comprises those patients who have a split second sound, the last component of which usually falls before the onset of filling. A "t" test done on these groups revealed statistical significance ($P > .01$) between onset of the third sound and onset of ventricular filling in all but the second group. Patients with third sounds associated with congenital heart lesions or chronic constrictive pericarditis were not included in this study. The type of classification given above appears to have clinical value in the evaluation of a patient with mitral valve disease prior to valvulotomy. This is especially true in persons with both a diastolic rumble and a systolic murmur, and in those patients in whom the cardiac catheterization data are equivocal. The following case history illustrates these points.

Case History.—I.M.M., a 22-year-old white woman with rheumatic heart disease, was admitted to the University Hospital in August, 1957, for evaluation of her cardiac lesion and for

possible mitral valvulotomy. She had experienced progressive cardiac disability since her third pregnancy. Physical examination revealed a totally irregular rhythm and a sustained precordial heave. There was a harsh, systolic murmur at the apex and left sternal border, an inconstant diastolic rumble, and a faint diastolic blow. A third sound was heard early in diastole, intermittently. The clinical opinion was that this patient had auricular fibrillation, mitral stenosis, a Graham Steell murmur, relative tricuspid insufficiency, and, probably, slight mitral insufficiency. The venous pressure was 80 mm. of saline; arm-to-lung circulation time was 11 seconds, and arm-to-tongue was 21 seconds. Cardiac catheterization revealed the following pressures: right atrium, 9/6; right ventricle, 40/5; pulmonary artery, 32.5/12.5; wedge, 27/11.5. After four minutes of

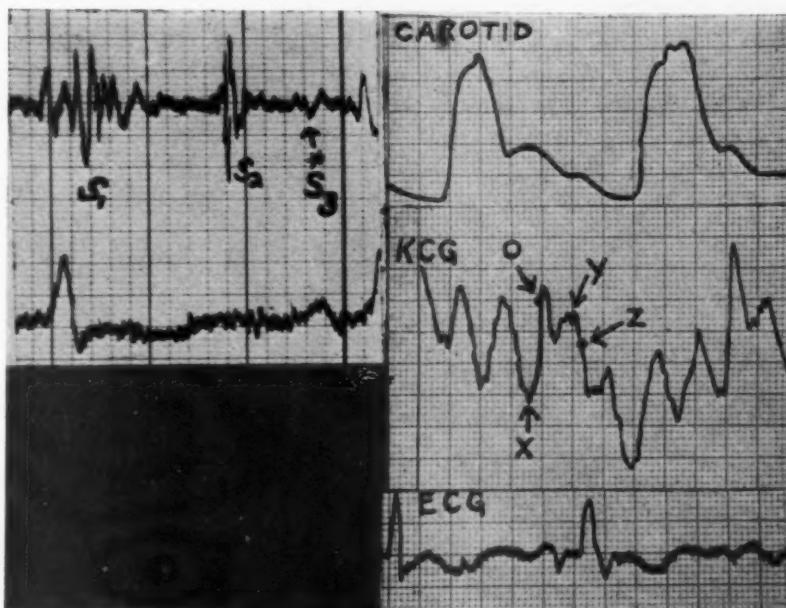


Fig. 1.—Subject R. L., with congestive heart failure. The protodiastolic gallop sound (S_3) occurs 0.07 second after the onset of ventricular filling (X arrow). Letter O denotes "peak" of filling phase. Letters Y and Z denote waves due to atrial contraction, and the phonocardiogram displayed an occasional atrial gallop sound which fell between Y and Z.

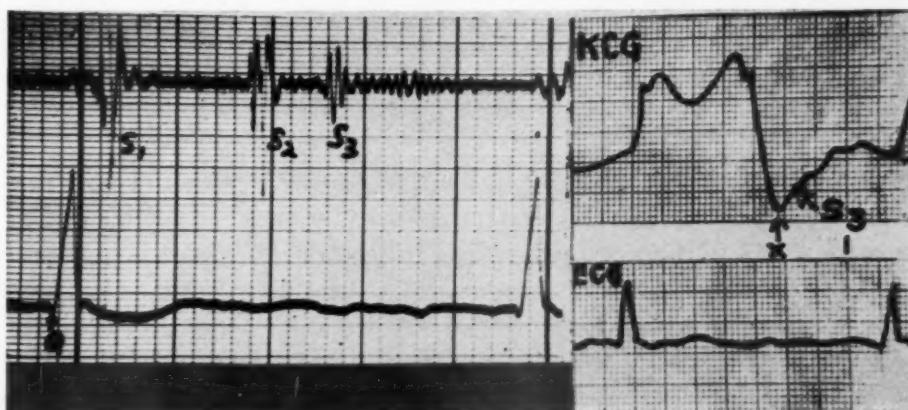


Fig. 2.—Subject I.M.M., with mitral insufficiency. The "ventricular gallop" third sound (S_3) occurs 0.06 second after onset of ventricular filling (X arrow).

exercise the wedge pressure rose to 61/41. The pressure data were considered to be consistent with combined mitral stenosis and mitral insufficiency. The final preoperative impression was that of a high degree of stenosis and some insufficiency.

At operation the heart was found to be enlarged, particularly the left ventricle. The left atrium was large and tense, with marked systolic expansion. The pulmonary artery was only slightly dilated, but the right ventricle was thought to be hypertrophied. The left auricle was entered, and a very much dilated annulus with a relatively normal mitral valve was found. There was a pronounced regurgitant jet, but no stenosis was present. The chest was closed and the postoperative course was without complications.

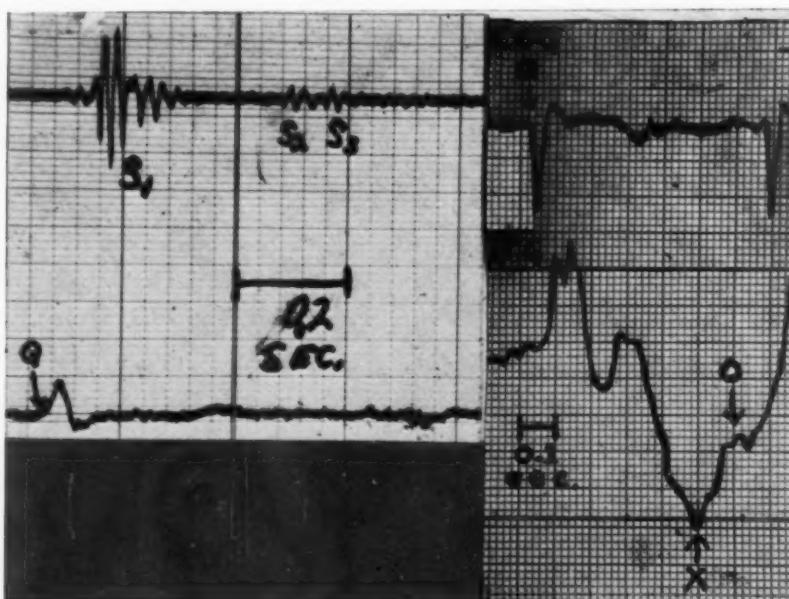


Fig. 3.—Subject G.B.R., with mitral stenosis. The "opening snap" third sound (S_3) occurs at the onset of ventricular filling (X arrow) rather than toward "peak" (O arrow).

Subsequent review of the preoperative phonocardiograms on this patient revealed systolic murmurs in all areas. In the mid-precordial, tricuspid, and mitral areas there was a third heart sound, followed by a diastolic rumble. Because of auricular fibrillation, no two cardiac cycles were of exactly the same length. However, average time intervals from at least fifteen cycles revealed that the third heart sound fell 0.06 second after the onset of ventricular filling (Fig. 2). Thus, this sound was not an opening snap, but was the ventricular gallop of insufficiency. Pre-operative evaluation of this patient's records in this manner could have prevented erroneous diagnosis.

Similar difficulty in making a clear auscultatory separation between the opening snap of mitral stenosis and other early diastolic third sounds is encountered frequently.⁹ Occasionally, difficulty is met in reading phonocardiograms alone. The ventricular gallop usually occurs later in diastole than does the opening snap, as is shown by the data in Table I. However, in one of our patients with "pure" mitral stenosis the opening snap came 0.12 second after the onset of the second heart sound, and in another patient with "pure" mitral insufficiency the ventricular gallop came 0.15 second after the second sound, a separation between the time of occurrence of these two extra sounds of only

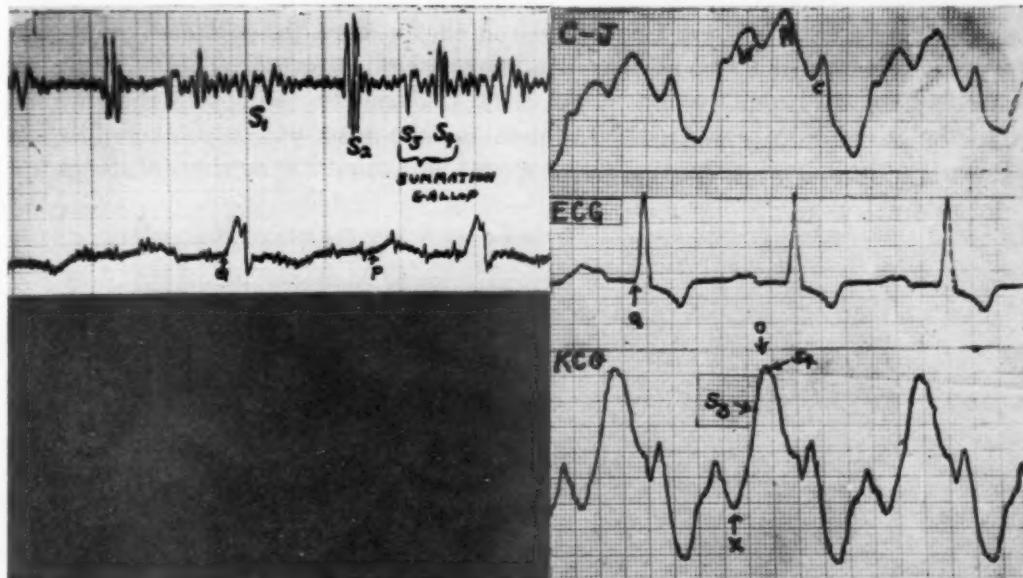


Fig. 4.—Subject E. K., with congestive heart failure. The summation gallop (S_3 and S_4) is heard as one sound with the stethoscope. The protodiastolic gallop (S_3) occurs 0.08 second after ventricular filling (X arrow). The atrial gallop portion (S_4) occurs 0.14 second after filling. Both sounds fall after the P wave. Note that the atrial wave (O arrow) is continuous with the curve of passive early ventricular filling.

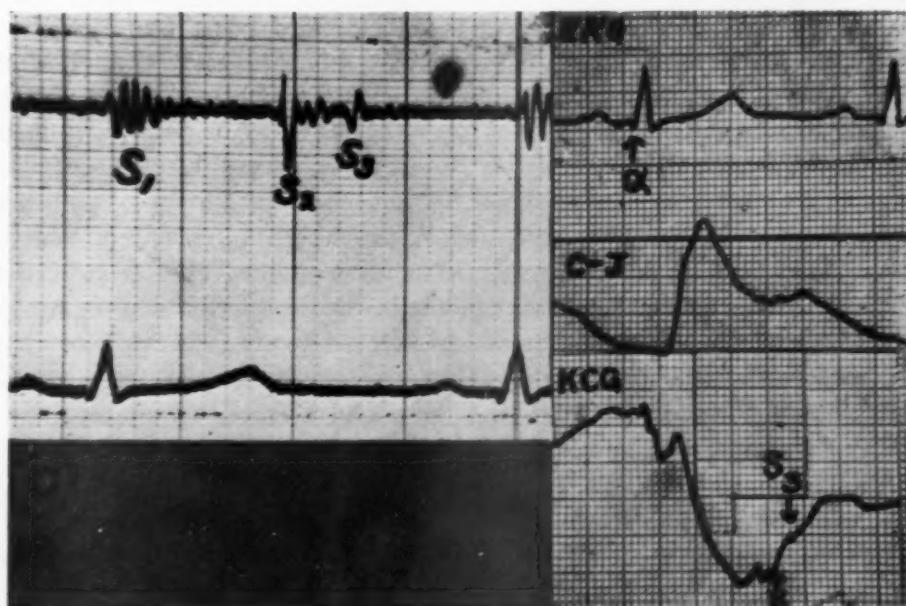


Fig. 5.—G. J., 23-year-old normal male subject. The physiologic third sound occurs after the onset of ventricular filling (X arrow).

0.03 second. It would be virtually impossible with the use of the stethoscope alone to differentiate these two sounds on the basis of time of occurrence. A larger series than that reported in this study would probably reveal a complete overlap between time of occurrence of these two sounds. It is with this in mind that the correlation between third sounds and the onset of ventricular filling, as shown by the kinetocardiogram, is proposed as a superior method of diagnosis.

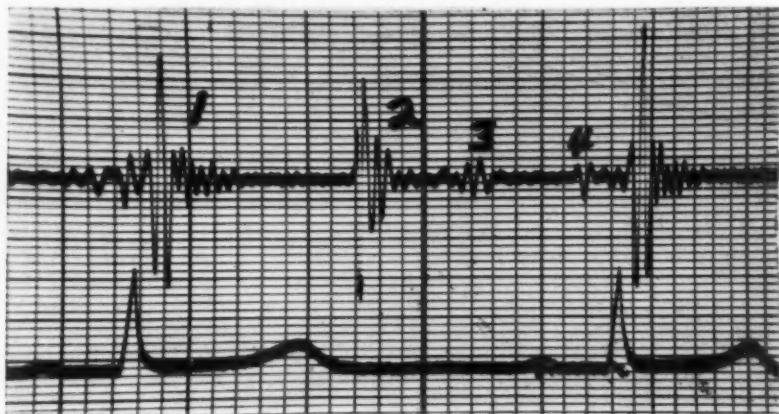


Fig. 6.—Phonocardiogram from V. M., a 17-year-old subject with no history or physical findings of cardiac disease. All four normal heart sounds are seen.

This present study also adds confirmatory evidence to the generally accepted idea of the genesis of the physiologic third heart sound. Earlier work, using the descent of the V wave in jugular pulse tracings as the criterion for onset of ventricular filling, indicated that this sound occurred after the peak of the V wave.¹⁰ From this it was deduced that the physiologic third heart sound occurs as a consequence of the force of rapid ventricular filling in early diastole and the vibrations of the atrioventricular septal structures which result from this force. Rushmer¹¹ has noted that the valves are either actively or passively tensed by the tendineae during all phases of the cardiac cycle, except during early diastolic filling, at which time they are under no tension. As early ventricular filling ends, the tendineae and cusps are again tensed, probably as a result of ventricular volume change. This sudden change in tension on the valvular structures is, in all likelihood, the most important factor in the production of the physiologic third heart sound. Our work has at least served to confirm the view that the sound occurs toward the end of the early diastolic ventricular filling phase. One recent study,¹² however, reported that the sound occurred simultaneously with the peak of the jugular V wave, and thus was interpreted as a "physiological opening snap." Pressure tracings taken from the surface of the jugular vein are rather variable in their reliability for timing purposes, however, and several previous studies have reported a lag of 0.04 to 0.06 second between jugular and atrial events.^{10,13} When this time lag is taken into consideration, the physiologic third sound falls well down on the descending limb of the V wave, indicating its occurrence after the onset of ventricular filling. The kinetocardiogram is, there-

fore, a more accurate guide to the onset of ventricular filling than are jugular pulse wave tracings.¹ The exact time of onset of ventricular filling is usually best recorded from the fifth or sixth intercostal spaces at the left parasternal line.

The slope and duration of the filling wave are important characteristics, as has been shown by Warren and co-workers.¹⁶ Augmented ventricular filling, as occurs with the high levels of venous pressure in congestive failure, produces waves of steep slope and short duration. Diminution of the rate of filling, as in mitral stenosis, produces waves of flat slope and prolonged duration.

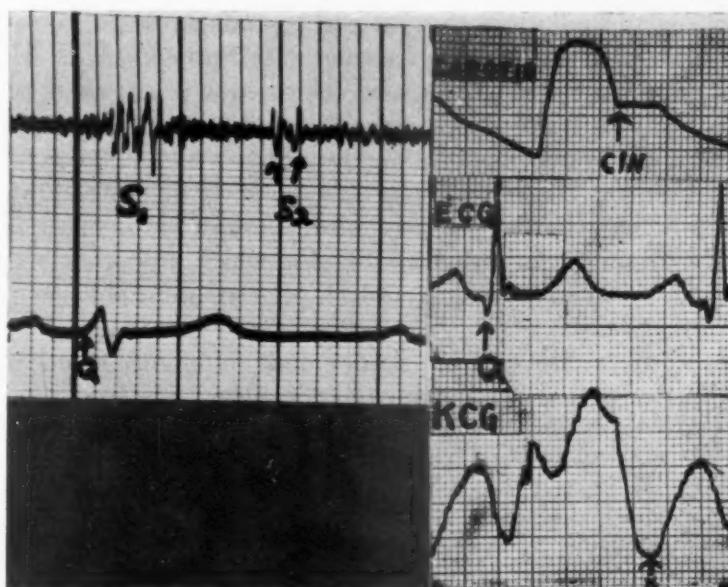


Fig. 7.—The tracings demonstrate a split second sound (S_2) which occurs with the carotid incisura (CIN) and 0.07 second before onset of ventricular filling (X arrow).

The filling of the two ventricles usually takes place almost simultaneously. There is, however, a slight "normal asynchronism" between the two sides. The atrial V peak and y descent on the right begins 0.02 second before that on the left, as is shown in some of Braunwald's tracings.¹⁴ The difference seems to be due to the increased duration of isometric relaxation of the left ventricle over the right. Moscovitz¹⁵ has recorded cycle phase time lengths in dogs and found that the period of isometric relaxation in the left ventricle lasts almost twice as long as the similar period in the right ventricle. Even though right ventricular ejection is longer than left, the total effect results in the delay in the V peak and y descent on the left. This minor difference in filling is not usually seen in kinetocardiographic tracings which display only one filling wave.

Previous work by Dock, Grandell and Taubman¹³ indicated that the protodiastolic gallop of congestive heart failure is an accentuated physiologic third heart sound. The results of this present study tend to confirm this view, since a comparison of these two sounds revealed that they have similar relationships to the onset of ventricular filling (Table I; Figs. 3 and 5).

SUMMARY

1. Phonocardiograms and kinetocardiograms were taken on subjects who displayed a third heart sound occurring in early diastole. A comparison of these records was made in order to obtain the relationship between these sounds and the onset of ventricular filling.

2. Correlation of these events indicated that the subjects fell into three general groups: (I) Those subjects in whom the diastolic sound occurred well after the beginning of ventricular filling. This group includes the normal subjects with a physiologic third sound, subjects with the ventricular gallop of mitral insufficiency, and subjects with the protodiastolic gallop of congestive heart failure unrelated to valvular lesions. (II) Subjects with mitral stenosis in whom the "opening snap" third sound coincided with the onset of ventricular filling. (III) Subjects with a split second sound, the last component of which fell before the onset of ventricular filling.

3. The timing of the relationship between early diastolic third sounds and the ventricular filling wave has proved clinically useful in the selection of patients for mitral valvulotomy. An instance is cited in which proper evaluation of these events would have prevented complete lack of correlation between preoperative and operative diagnosis.

4. This study confirms previous work done to determine the genesis of the physiologic third heart sound and its relationship to the protodiastolic gallop of congestive heart failure.

REFERENCES

1. Norman, J., and Harrison, T. R.: Movements and Forces of the Human Heart. IV. Precordial Movements (Kinetocardiograms) in Relation to Ejection and Filling of the Ventricles, *A.M.A. Arch. Int. Med.* **101**:582, 1958.
2. Luisada, A. A., and Aravanis, C.: Phonocardiography as a Clinical Method of Examination, *Med. Clin. North America* **41**:235, 1957.
3. Eddleman, E. E., Jr., Willis, K., Reeves, T. J., and Harrison, T. R.: The Kinetocardiogram. I. Method of Recording Precordial Movements, *Circulation* **8**:269, 1953.
4. Eddleman, E. E., Jr., and Willis, K.: The Kinetocardiogram. II. The Normal Configuration and Amplitude, *Circulation* **8**:370, 1953.
5. Dressler, W.: Pulsations of the Walls of the Chest, *Arch. Int. Med.* **60**:225, 1937.
6. Mounsey, P.: The Opening Snap of Mitral Stenosis, *Brit. Heart J.* **15**:135, 1953.
7. Contro, S.: Ventricular Gallop in Mitral Stenosis. Its Mechanism and Significance, *Am. HEART J.* **54**:246, 1957.
8. Wood, P. H.: Diseases of the Heart and Circulation, Ed. 2., Philadelphia, 1956, J. P. Lippincott Co.
9. Williams, J. A., Litman, D., and Warren, R. W.: Experiences With the Surgical Treatment of Mitral Stenosis, *New England J. Med.* **258**:13, 1958.
10. Orias, O., and Braun-Menendez, E.: The Heart Sounds in Normal and Pathological Conditions, New York, 1939, Oxford University Press.
11. Rushmer, F. R., Finlayson, B. L., and Nash, A. A.: Movements of the Mitral Valve, *Circulation Res.* **4**:337, 1956.
12. Eddleman, E. E., Jr., Willis, K., Walker, R., Christianson, L., and Pierce, R.: The Relationship of the Physiologic Third Heart Sound to the Jugular-Venous Pulse, *Am. J. Med.* **17**:15, 1954.
13. Dock, W., Grandell, F., and Taubman, F.: Physiologic Third Heart Sound: Its Mechanism and Relation to Protodiastolic Gallop, *Am. HEART J.* **50**:449, 1955.
14. Braunwald, E., Fishman, A., and Cournand, A.: Time Relationship of Dynamic Events in the Cardiac Chambers, Pulmonary Artery, and Aorta in Man, *Circulation Res.* **4**:100, 1956.
15. Moscovitz, H. L., and Wilder, R. J.: Pressure Events of the Cardiac Cycle in the Dog: Normal Right and Left Heart, *Circulation Res.* **4**:574, 1956.
16. Warren, J. V., Leonard, J. J., and Weisler, A. M.: Gallop Rhythm, *Ann. Int. Med.* **48**:580, 1958.

Case Reports

Myocardial Disease Associated With Progressive Muscular Dystrophy (A Report of 2 Cases)

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INTRODUCTION

The fact that cardiac involvement may accompany progressive muscular dystrophy has been recorded previously.^{1,2} The incidence is believed to vary from 50 to 85 per cent, depending upon the type, severity, and distribution of the lesions involving the skeletal muscle.³

The clinical manifestations of the myocardial complication consist mainly of various arrhythmias, heart failure, generalized cardiomegaly, and nonspecific electrocardiographic abnormalities.⁴ These may persist during prolonged disability or, particularly when the juvenile type of muscular dystrophy is present, may terminate in an early fatal outcome. In either event the symptoms and objective findings are quite similar to those encountered in other more common types of severe heart disease.

These diagnostic and prognostic obscurities always prompt a re-examination of the problem whenever the analysis of new clinical material makes it possible. In accordance with this view the present report records the details encountered in two patients with muscular dystrophy and cardiac myopathy.

CASE REPORTS

CASE 1.—P. R., a 19-year-old white boy, was admitted to the Hahnemann Medical College and Hospital on March 19, 1954. A year prior to hospitalization the patient noted exertional dyspnea, hemoptysis, and peripheral edema.

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A diagnosis of anterior poliomyelitis had been made when the patient had a severe febrile illness at 9 months of age. This disease was considered responsible for the odd gait which developed when he first walked, and which persisted throughout his adult life. A heart murmur was said to have been discovered at age 15. At the time of admission, examination of the heart revealed a blood pressure of 108/88 mm. Hg, and normal sinus rhythm. Although no murmurs were heard, the pulmonic second sound was accentuated and reduplicated.

The typical stigmata of pseudohypertrophic muscular dystrophy were observed on neurological examination. A moderate degree of atrophy was noticed about the shoulder girdle, particularly involving the supraspinatus, the rhomboids, and the serratus anterior muscles. The pectoralis muscles were weak. The patient walked with a characteristic waddling gait and arose from a sitting position on the floor by "climbing up his legs." A lordosis compensated for the weakness of the posterior spinal muscles. The thigh muscles were atrophied and weak as compared to the distal musculature.

Laboratory examination of the blood and urine failed to reveal any abnormality except a creatinuria which averaged 72.5 mg. per 24 hours.

T-wave inversions in Leads I, aVL, V₅, and V₆ were discovered electrocardiographically. In addition, Q waves were present in Leads I and aVL, and the P waves were broadened and peaked in Lead II. These findings were interpreted as strongly suggestive of myocardial abnormality (Fig. 1).

The heart was moderately enlarged on x-ray examination (Fig. 2).

No intracardiac communications or vascular shunts were uncovered by right heart catheterization. The pressures in the venae cavae, right atrium, and right ventricle were normal.

Biopsy of the right gastrocnemius muscle was performed. Microscopic examination revealed variations in the size of the individual muscle fibers, atrophy, and fibrous tissue replacement. These findings were considered compatible with progressive muscular dystrophy (Figs. 3 and 4).

At the time of a thoracotomy, which definitely eliminated the possibility of any undisclosed but remediable valvular lesions, or vascular shunt, a biopsy of the left atrial and left ventricular muscles was performed.

Examination of the atrial muscle disclosed subendocardial fibrosis of the acellular type and focal areas of fibrosis associated with fatty infiltration adjacent to the subepicardium. In addition, there was interstitial edema and vacuolization of the myofibrils (Figs. 5 and 6).

Degeneration of muscle fiber, fibrosis, and an acute inflammatory exudate consisting of neutrophils, lymphocytes, and monocytes were noted when the ventricular biopsy material was examined. The sarcoplasm of the individual fibers was characterized by clumping (Figs. 7 and 8).

The findings in the atrial and ventricular muscles were considered compatible with the cardiac myopathy observed with progressive muscular dystrophy.^{5,6}

The patient's postoperative course was uneventful. He expired at home suddenly three months later. An autopsy was not obtained.

CASE 2.—A. L., a 58-year-old white woman, has been observed in private practice by one of the authors (P. L.).

Anterior poliomyelitis was believed to have occurred during the patient's childhood, and subsequently she had difficulty in walking.

Congestive heart failure developed when she was 32 years of age and in the last trimester of her first pregnancy. This recurred six years later during a second pregnancy. From that point on, exertional dyspnea and peripheral edema persisted.

Examination of the heart revealed a blood pressure of 150/90 mm. Hg, and a normal sinus mechanism which was interrupted by numerous premature ventricular contractions. The mitral first sound was reduplicated, and a Grade 2 blowing systolic apical murmur was present.

Moist râles were heard at both pulmonary bases, and the liver was persistently enlarged two fingerbreadths or more below the right costal border.

The patient had a waddling gait and "climbed up the legs" in order to arise from a sitting position. The facial, scapular, and both gastrocnemius muscles were atrophied.

Flattened and inverted T waves were observed in the electrocardiogram in Leads I, II, aVL, aVF, V₅, and V₆. The P waves were abnormal in Leads I and II.

Generalized cardiac enlargement was observed on x-ray examination (Fig. 9).

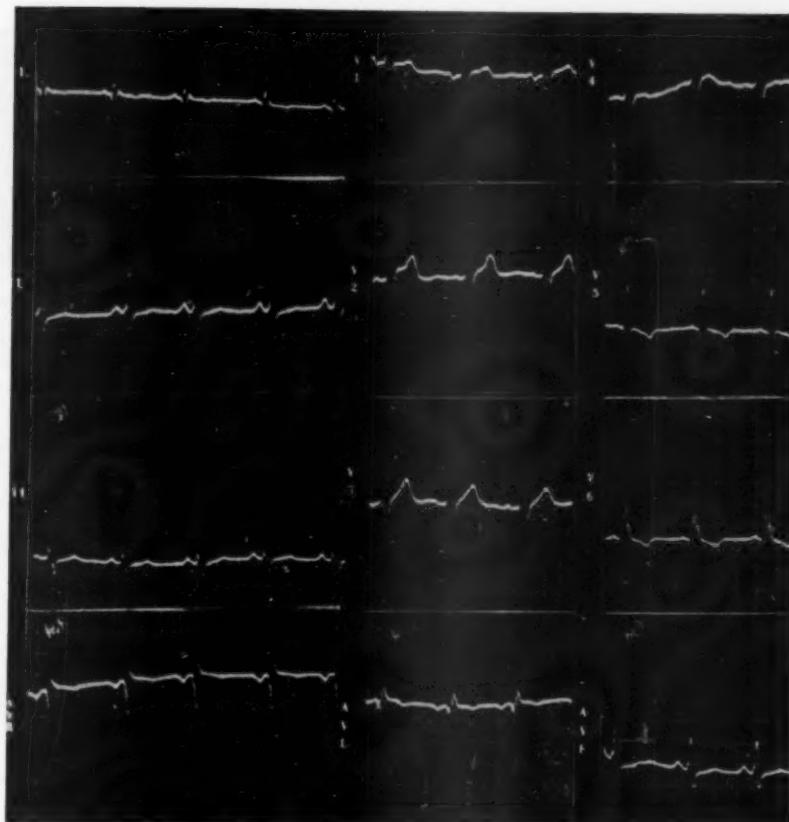


Fig. 1.—Electrocardiogram of Case 1.

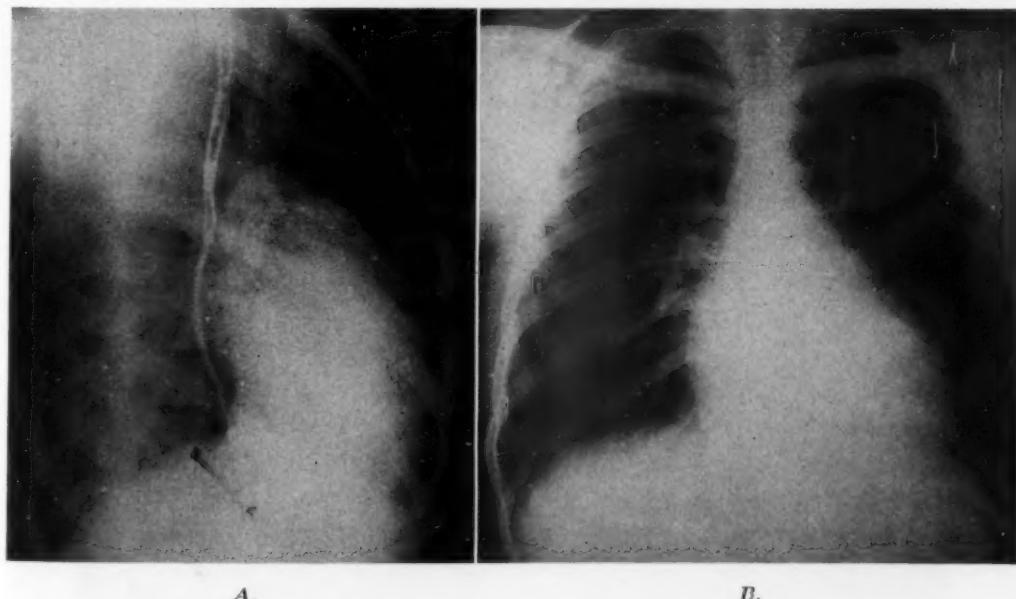


Fig. 2.—X-ray film of chest of Case 1. A, Right anterior oblique view with barium swallow.
B, Posteroanterior view.

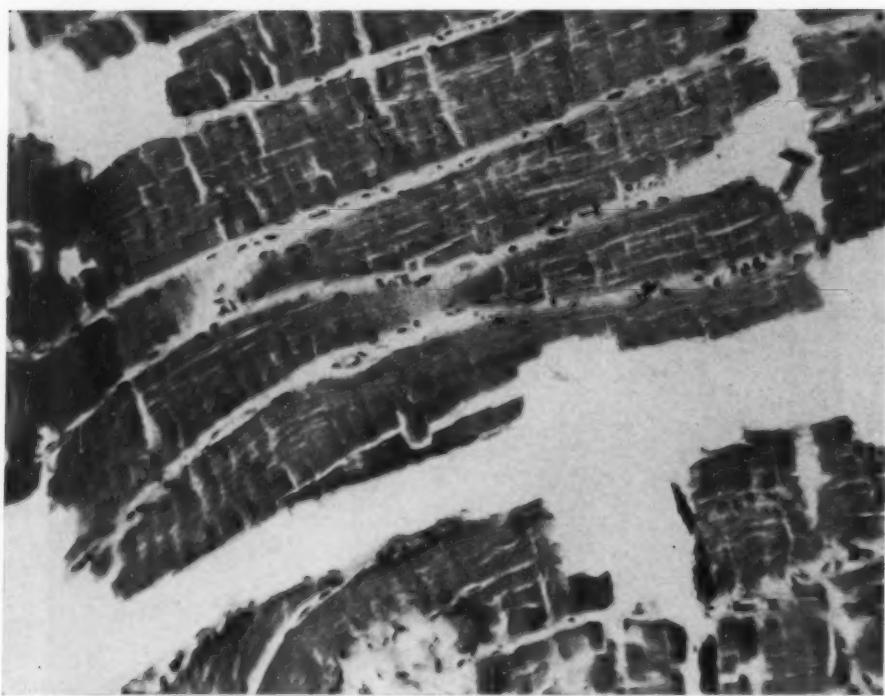


Fig. 3.—Gastrocnemius muscle showing atrophy of muscle fiber.



Fig. 4.—Gastrocnemius muscle showing sarcolemmic nuclear proliferation.

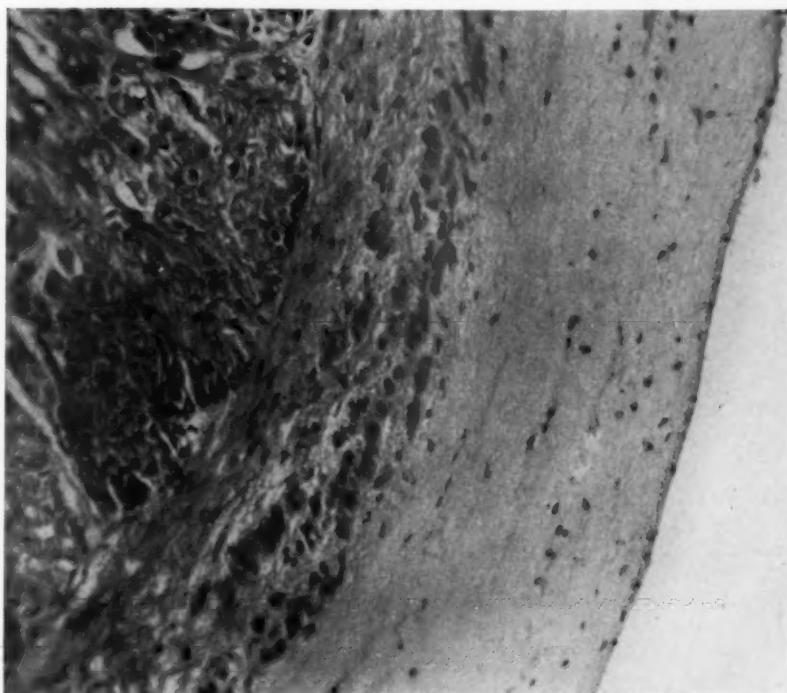


Fig. 5.—Auricular muscle showing subendocardial fibrosis.

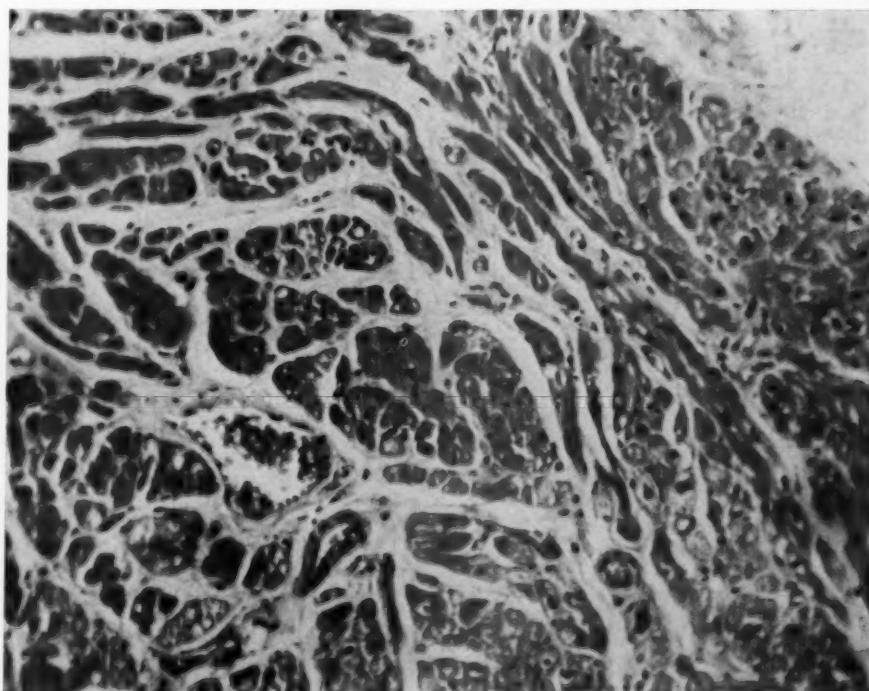


Fig. 6.—Auricular muscle showing interstitial edema with vacuolization of the myofibrils.

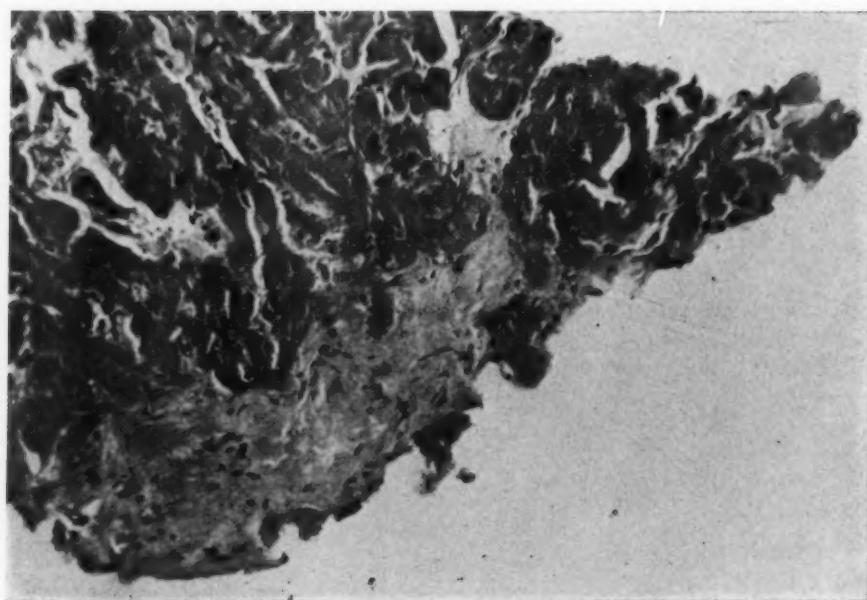


Fig. 7.—Ventricular muscle. Area of fibrosis.

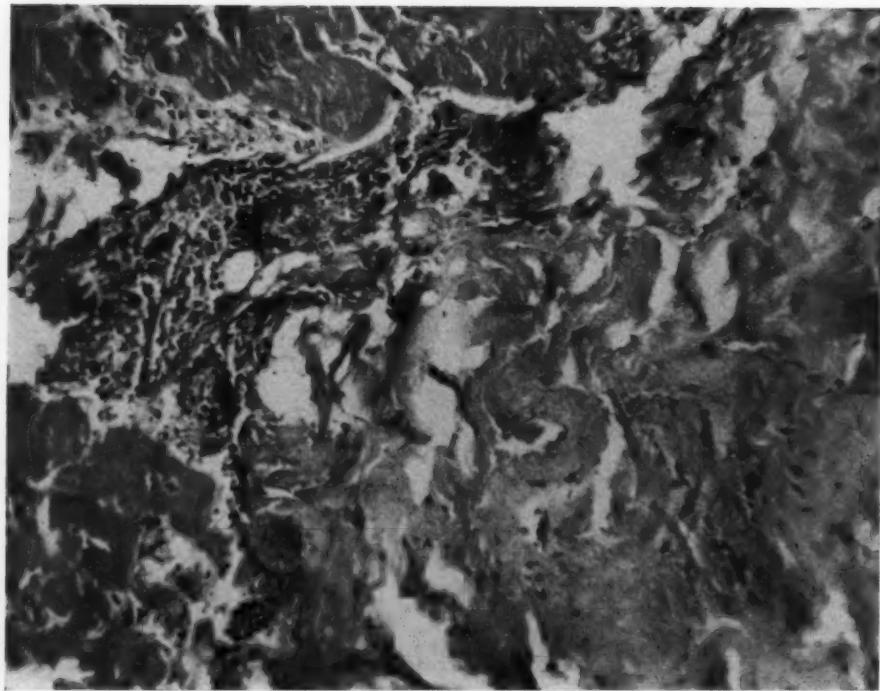
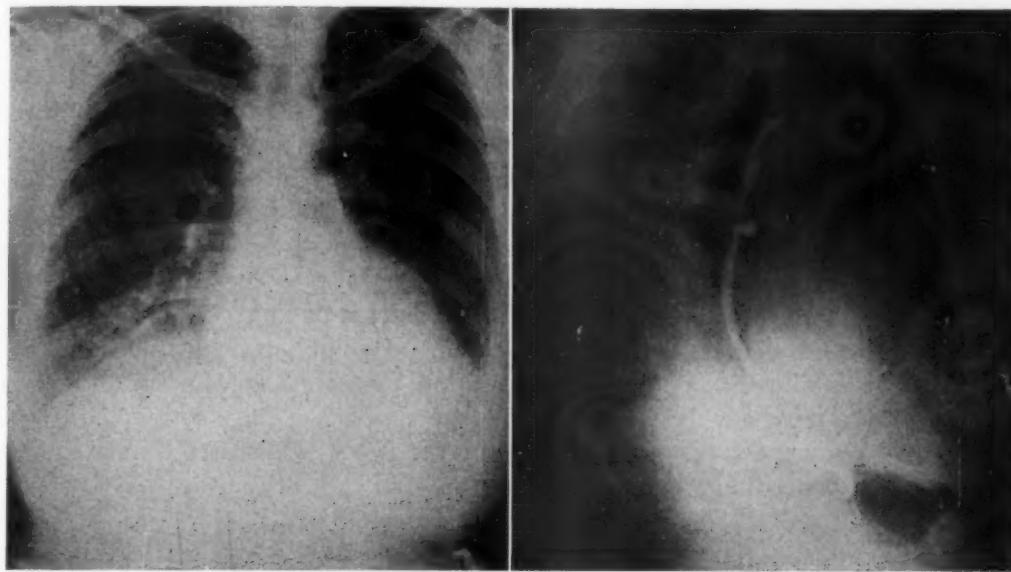


Fig. 8.—Ventricular muscle. Acute inflammatory exudate.

The microscopic examination of biopsy material from the left gastrocnemius muscle indicated old focal necrosis consistent with progressive muscular dystrophy.

In spite of the duration of the clinical manifestations the patient responded to the ordinary measures for the control of congestive heart failure and is still living and relatively well.



A.

B.

Fig. 9.—X-ray film of chest of Case 2. A, Posteroanterior view. B, Right anterior oblique view with barium swallow.

DISCUSSION

A consideration of the patients herein reported appears to confirm and extend current concepts pertaining to the association of myocardial disease with progressive muscular dystrophy.

Progressive muscular dystrophy usually develops in infancy or early childhood. This onset may be confused with anterior poliomyelitis as a wasting muscular disease, because it occurs at an age when polio virus infections are most common.

Unpredictable intervals may separate the involvement of the skeletal muscles from the onset of the cardiac symptoms. However, since the latter frequently arise late, only after the heart has failed, the relationship of the progressive muscular dystrophy to the cardiac disability may be quite obscure.

Under the circumstances, and with the present case reports serving as illustrations, it is pertinent to suggest that when a patient with a past history of a wasting muscular disease subsequently develops significant cardiac disability, a single disorder, namely, progressive muscular dystrophy, may be responsible for the entire syndrome.

Objective findings include the usual muscular wasting and pseudohypertrophy of muscle groups classically described for the various types of this disease

entity. The very striking "climbing up the legs" (Gower's sign) should aid in making this diagnosis. Biopsy of the muscles of the involved areas usually will confirm the presence of progressive muscular dystrophy.

There are no diagnostic electrocardiographic patterns. Abnormal rhythms and nonspecific T-wave changes are not unusual. Cardiomegaly is generalized and compatible with that seen in coronary heart disease accompanied by heart failure.

The most striking feature of the two cases presented is the marked contrast in prognosis between different types of the same disease process. The so-called juvenile or pseudohypertrophic progressive muscular dystrophy usually ends fatally, most commonly with cardiac failure, when the patient is about 20 years of age. On the other hand, the facio-scapulohumeral type is compatible with longer life, even extending into the sixth decade despite the presence of congestive heart failure of long duration. As a matter of fact, the presence of a muscular wasting disease existing from childhood or puberty with chronic congestive heart failure in a middle-aged woman strongly suggests the diagnosis of progressive muscular dystrophy.

Therapeutic measures are successful in the types of diseases that are compatible with longer life.

SUMMARY

Two cases of progressive muscular dystrophy involving the heart are reviewed. The clinical, historical, laboratory, and pathophysiologic aspects are presented. A discussion of the diagnosis and prognosis of this esoteric disease of the heart stresses that a high index of suspicion should exist when a muscular wasting disease is associated with congestive heart failure.

REFERENCES

1. Zatuchni, J., Aegeuter, E. E., Molthan, L., and Shuman, C. R.: The Heart in Progressive Muscular Dystrophy, *Circulation* **3**:846, 1951.
2. Bevan, H.: Changes in the Musculature of the Gastrointestinal Tract and in the Myocardium in Progressive Muscular Dystrophy, *Arch. Path.* **40**:225, 1945.
3. Berenbaum, A. A., and Horowitz, W.: Heart Involvement in Progressive Muscular Dystrophy, *AM. HEART J.* **51**:622, 1956.
4. Manning, G. W., and Cropp, G. J.: The Electrocardiogram in Progressive Muscular Dystrophy, *Brit. Heart J.* **20**:416, 1958.
5. Globus, J. H.: The Pathologic Findings in the Heart Muscle in Progressive Muscular Dystrophy, *Arch. Neurol. & Psychiat.* **9**:59, 1923.
6. Cohen, S.: Myocardial Fibrosis in Progressive Muscular Dystrophy, *J. Med.* **17**:21, 1936.

Paradoxic and Knotted Embolism

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Paradoxic embolism is the passage of an embolus from the venous into the arterial system by way of an abnormal shunt. Conceivably, almost any such vascular abnormality could render possible the transfer of an embolus. Actually, however, this has taken place in nearly all recorded cases through an open foramen ovale. The term "paradoxic embolism," it is said, was coined by Zahn.¹ Less common synonyms are: "consecutive embolism," "crossed embolism," "aberrant embolism."

Johnson,¹ in 1951, reviewed the literature and found only 41 confirmed cases, including one of his own, in which an embolus was lodged within the foramen ovale. Fruhling and Marcoux,² in 1953, reported the astounding number of 6 personal cases, including one of ductus arteriosus embolism. With 3 additional reports³⁻⁵ and our own, the number of verified cases of paradoxic embolism recorded to date totals 51.

In a second group, classified by Johnson as "presumptive," the case reports are more numerous.⁶⁻⁸ In these cases the diagnosis is usually based on the triad of venous thrombosis, open foramen ovale, and arterial embolism, without the evidence of an embolus trapped while passing the foramen ovale.

For the development of a paradoxic embolism three conditions must exist: (1) embolus of venous origin, (2) open foramen ovale, and (3) reversal of the pressure gradient between the atria.

1. Emboli from venous thrombosis represent the most common type of embolism. Substances other than blood clot also can serve as emboli. In a number of more or less convincing cases of embolism, various materials have been described, including tissue fragments from liver, cerebellum, tumors, and fat, as well as air and foreign bodies. A nut-sized shrapnel fragment was recovered from the left ventricle after gunshot injury of the leg.⁹

2. Patency of the foramen ovale is of two types: (a) anatomic patency (foramen ovale guarded or protected by a valve, "valvular patency"), and (b) physiologic patency (unguarded or unprotected foramen ovale, "two-way patency"). In an unselected series of 1,100 consecutive autopsies, Thompson and Evans¹⁰ found the foramen ovale patent for a probe (0.2 cm.) in 319 cases (29

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per cent), and patent for a pencil (0.7 cm.) in 67 cases (6 per cent). Patten¹¹ encountered an open foramen ovale in 21 per cent of 4,000 unselected autopsies. Thus, 20 to 33 per cent of the human race are afflicted with some degree of patency of the foramen ovale, so that it might appear more relevant to consider the anatomic patency of the foramen ovale in the adult as a condition within the range of normal, rather than as a congenital anomaly. Physiologic patency (foramen ovale unguarded by a valve) is uncommon. The rarest congenital lesion of the foramen ovale is congenital atresia.¹¹

3. Normally, the pressure in the left atrium is higher than that in the right. This insures continuous closure of an anatomically patent foramen ovale. If the pressure in the right atrium rises above that in the left, the flap of the septum opens readily and blood is released from the right into the left atrium. This one-way valve action depends upon the flexibility of septum I, functioning as a mobile diaphragm, and the rigidity of septum II, forming a firm console. Pliability of septum II would permit blood flow from the left to the right. Obstruction of pulmonary arteries leads to a rise in pressure in the right heart. This is usually caused by pulmonary embolism. Forty-one of the 51 confirmed cases of paradoxical embolism were combined with pulmonary embolism or infarction. Another cause of increased right intra-atrial pressure is myocardial insufficiency. The general passive venous congestion of cardiac decompensation must be combined with, if not preceded by, a pressure rise in the right atrium. Then, blood can flow through an open foramen ovale, and some writers⁷ attribute an alleviating function to this mechanism, relieving the venous congestion.

Johnson lists as a fourth condition necessary for paradoxical embolism an "imponderable element of chance by which the embolus passes through the foramen ovale instead of up the pulmonary artery." The chances, of course, will increase with the amount of the foraminal blood flow, which, in turn, is a function of the pressure gradient and the size of the foramen.

For designating an embolus in the arterial system as paradoxical, two criteria should be considered: (1) evidence that the embolus derived from the venous system, excluding the possibility of its formation in the arterial system, and (2) an embolus so large that it could not have passed through the pulmonary circulation. These criteria, although seemingly commonplace, have not been met in all instances. After strict selection it appears that a number of the presumptive cases have been diagnosed too precipitately, especially when "generalized arteriosclerosis" was one of the autopsy findings. Thrombosis of an arteriosclerotic vessel in a patient with circulatory insufficiency is common, and it may be impossible to distinguish between local thrombosis and embolism in vessels as small as the cerebral arteries or branches of the renal arteries. This applies particularly to those instances in which infarcts of various organs were thought to be paradoxical for no other reason than concomitant venous thrombosis and an open foramen ovale. Only when the size and shape of the clot betray its venous origin can the diagnosis of paradoxical embolism be made. The diagnosis cannot be doubted in instances in which materials other than blood clot (foreign bodies, tissue fragments, gases, liquids) functioned as emboli and were of venous origin.

The term *paradoxic* has also been used to label a brain abscess occurring with a certain frequency with congenital heart disease.^{12,13} It was thought that an interatrial or interventricular septal defect especially facilitated the transit of bacteria or infectious material from a venous focus into the arterial system. This route's importance in disseminating infections appears negligible, considering the size of bacteria and the diameter of the pulmonary capillary, unless a mysterious, as yet unproved filter mechanism for bacteria is ascribed to the pulmonary circulation.

Below, I present a case of paradoxic embolism. The case includes as an additional unique phenomenon the knotting of two emboli, which, to my knowledge, has never before been reported. A single embolus with a true knot has been described by Adelson.¹⁴

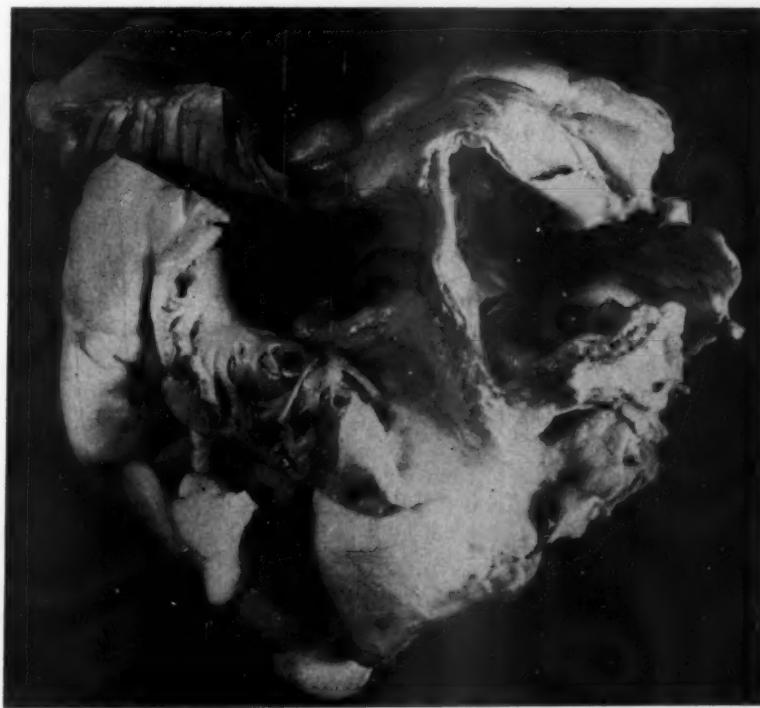


Fig. 1.—Photograph of heart with paradoxic embolus. Only the proximal end of the clot, lodged in the foramen ovale, is shown in this view. The shorter segment of the embolus protrudes into the left atrium.

CASE REPORT

A 55-year-old Negro woman suffering from hypertension and chronic alcoholism was admitted in June, 1957, because of progressive mental deterioration following a "stroke." Her blood pressure was difficult to control and fluctuated from 142/88 to 210/120 mm. Hg. In July and again in October, 1957, she experienced two episodes with weakness of her right limbs, slurring of speech, and facial twitching. In December, 1957, several brief seizures occurred, with loss of consciousness and convulsions. In April, 1958, she complained of sudden "tightness" in her chest, inability to breathe, and pain in the left arm, and also was cold and clammy.

On Oct. 25, 1958, following a few days of a slight fever (100.4°F.), she had chest pain in the sternal area, radiating into the epigastrium. The next day she developed a persistent cough and dyspnea. Blood pressure then was 120/100 mm. Hg and the pulse rate 100. October 28, she died after a 30-minute period of marked cardiac arrhythmia.

At autopsy, massive bilateral pulmonary thrombosis was found, occluding 60 to 70 per cent of the pulmonary arteries. No infarcts of the lungs were noted.

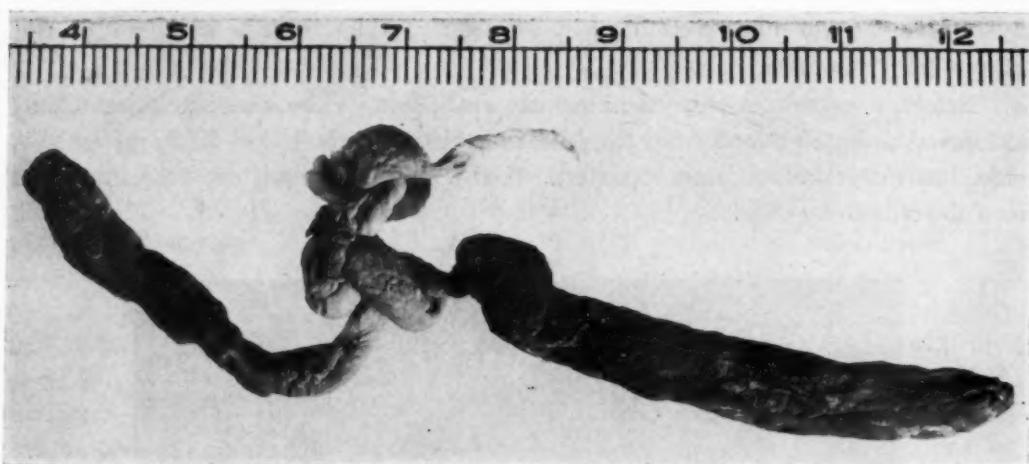


Fig. 2.—Close-up photograph of the middle third of the cardiac embolus, to demonstrate the cluster of knots, where 2 separate emboli were knotted together by their terminal ramifications. Scale in centimeters.

The heart was enlarged and weighed 420 grams. The right coronary artery was occluded by a tan-grey, organized thrombus. In the left ventricular wall there was an old greyish-white posterior infarct, measuring 3 by 5 cm. The foramen ovale was anatomically patent (0.7 cm.), and firmly wedged in it there was the end of a long cylindrical embolus, which protruded 1 cm. out into the left atrium (Fig. 1). The larger portion of the embolus, extending into the right heart, contained, approximately 6 cm. from the foramen ovale, a cluster of knots (Fig. 2) and then continued into the right ventricle, doubled up, and reached the pulmonary conus. The over-all length of the embolus was 32 cm., and its thickness ranged from 0.3 to 1.0 cm. It was variegated grey and dark red, partially laminated, and had a rippled surface. When the cluster of knots was carefully reconstructed, it was found, somewhat surprisingly, that at this point two separate emboli were knotted together at their terminal ramifications, one possessing two, the other three branches. In addition to twisting, at least five true knots were present.

The brain (1,140 grams) contained a large area of tan-yellow malacia with beginning cyst formation, involving large portions of the left parietal, temporal, and occipital lobes.

No recent infarcts were encountered, and dissection of the venous system, including the legs, failed to reveal recent thrombosis.

The final anatomic diagnoses were: massive pulmonary thrombosis, pulmonary edema, paradoxical embolism of foramen ovale, marked generalized arteriosclerosis, old thrombosis of right coronary artery, old posterior infarct of heart, hypertrophy of heart, old large infarct of brain, stasis dermatitis of legs.

COMMENT

The sequence of events—peripheral thrombosis, pulmonary embolism followed by massive thrombosis, and paradoxical embolism—appears, in retrospect, to be well reflected in the patient's clinical course of initial slight fever, sudden

chest pain with progressive cough, and abrupt onset of arrhythmia 30 minutes before death. The open foramen ovale might very well have helped relieve the congestion in the right heart, thus prolonging her life over more than 3 days. When this shunt was abruptly occluded by the paradoxical embolus, acute cardiac insufficiency followed.

The size of the two knotted emboli indicates that they came from thrombosed leg veins. The knotting itself, in all probability, took place in the heart after the first embolus became lodged in the foramen ovale. It was made possible by the terminal ramifications of the clots. The remaining free end of the second embolus then was carried on into the right ventricle, and because of the constant traction and torsion of the blood stream the knots were pulled tight. That the knotting occurred in the vena cava is quite improbable, not only because of the questionable mechanics of such an incident in this location, but also because of the perfect timing that would be required for the simultaneous arrival of the two clots in this vessel.

SUMMARY

1. The entity of paradoxical embolism is defined and a brief review of the literature is made. The total number of verified cases reported to date is 51.
2. The conditions necessary for the development of paradoxical embolism are discussed. Two criteria to be considered before diagnosing an embolus in the arterial system as paradoxical are postulated.
3. A case is presented in which an embolus, consisting of two knotted thrombi, was lodged in the foramen ovale.
4. The knotting of two blood clots is unique and the present report appears to be the first describing this phenomenon.

REFERENCES

1. Johnson, B. I.: Paradoxical Embolism, *J. Clin. Path.* **4**:316, 1951.
2. Fruhling, L., and Marcoux, F.: L'embolie paradoxale; à propos de 6 observations personnelles, *Arch. mal. coeur* **46**:1013, 1953.
3. Young, R. L., Derbyshire, R. C., and Cramer, O. S.: Paradoxical Embolism: Review of Literature With Report of Case in Which This Condition Followed Administration of Dicumarol, *Arch. Path.* **46**:43, 1948.
4. Bigelow, N. H.: Paradoxical Embolism, *Am. J. Med.* **14**:648, 1953.
5. Robinson, F. J.: Lodging of an Embolus in a Patent Foramen Ovale, *Circulation* **2**:304, 1950.
6. Sauer, H. H.: Paradoxical Embolism in Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* **62**:906, 1955.
7. Ross, C. A., and Sprague, P. H.: A Case of Paradoxical Embolism, *AM. HEART J.* **36**:772, 1948.
8. Keeley, J. L.: Paradoxical Embolism, *Angiology* **8**:528, 1957.
9. Specht: Granatsplitter im linken Ventrikel nach Verletzung der Vena Femoralis, *Muenchen. med. Wchnschr.* **64**:892, 1917.
10. Thompson, T., and Evans, W.: Paradoxical Embolism, *Quart. J. Med.* **23**:135, 1930.
11. Patten, B. M.: Developmental Defects at the Foramen Ovale, *Am. J. Path.* **14**:135, 1938.
12. Abbott, M. E., Lewis, D. S., and Beattie, W. W.: Differential Study of a Case of Pulmonary Stenosis of Inflammatory Origin (Ventricular Septum Closed) and Two Cases of (a) Pulmonary Stenosis and (b) Pulmonary Atresia of Developmental Origin With Associated Ventricular Septal Defect and Death From Paradoxical Cerebral Embolism, etc., *Am. J. M. Sc.* **165**:636, 1923.
13. Hanna, R.: Cerebral Abscess and Paradoxical Embolism Associated With Congenital Heart Disease, *Am. J. Dis. Child.* **62**:555, 1941.
14. Adelson, L.: Knotted Cardiopulmonary Embolus, *Am. J. Clin. Path.* **25**:1285, 1955.

Postural Hypotension Following Dorsal Sympathectomy in Coarctation of the Aorta: Correction by Resection of the Coarctation

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In 1945, Gross¹ and Crafoord² introduced operative resection for coarctation of the aorta, with relief of the hypertension in a great majority of the cases. Prior to this time sympathectomy had proved to be ineffective in lowering the blood pressure of these patients.

In 1955, we had the opportunity to study a patient with coarctation of the aorta who had had a bilateral dorsal sympathectomy performed 10 years previously in another hospital. The hypertension was unaltered by the procedure, except that the patient developed severe postural hypotension. The response to resection of the coarctation was dramatic, with relief of both the hypertension and hypotension. Since, to our knowledge, these circumstances are unique, it seemed desirable to report the case in some detail.

CASE REPORT

A 34-year-old white woman was admitted to The George Washington University Hospital on Sept. 17, 1955, complaining of severe dizziness, fainting on standing, frequent severe headaches, and visual difficulty. Hypertension had been discovered in 1943, during the second trimester of pregnancy. A therapeutic abortion was advised, but was refused by the patient. She was placed at bed rest for the duration of the pregnancy and an uneventful cesarean section and tubal ligation were performed at term.

In 1945, because of the persistence of hypertension, a bilateral dorsal sympathectomy was performed, with removal of the third through the twelfth thoracic ganglia. The hypertension was unaffected and severe postural hypotension developed. The systolic blood pressure levels ranged from 180 to 200 mm. Hg when the patient was recumbent. Syncope upon standing was uncontrollable until she was fitted with a tight corset. During the next 10 years any attempt to get along without the corset was unsuccessful. She continued to have episodic headaches and a general lack of well-being. Antihypertensive drugs were used intermittently without response.

The patient recalled that a pulsating swelling in the front of the neck had been brought to her attention by a grade school teacher. This swelling remained essentially unchanged over the years and was asymptomatic.

On physical examination the patient was a well-developed and fairly well-nourished white woman who appeared to be her stated age. The blood pressure, while the patient was recumbent,

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was 200/125 mm. Hg in the arms and 180/110 mm. Hg in the legs. Several attempts were made to record the blood pressure with the patient standing, without the corset, but prompt syncope occurred and a measurement could not be obtained.

The most striking physical finding was a pulsating, tubular mass in the suprasternal notch. The mass was approximately 1.5 by 3 cm. in size. It appeared to originate beneath the right sternocleidomastoid muscle. There were palpable pulsations and a systolic bruit over both suprascapular regions. The heart was not enlarged and the lung fields were clear. A soft, Grade 2 systolic murmur was heard along the left sternal border. The murmur was not transmitted into the axilla and could not be heard in the back. The femoral pulsations were delayed and markedly diminished. The dorsalis pedis and posterior tibial pulses were not remarkable. The ocular fundi were normal.

A heart film showed prominence of the left ventricle, without definite enlargement. The aortic knob was small. There was no rib notching. Electrocardiograms were found to be within normal limits. Studies of the blood and urine gave essentially normal results.

An angiogram revealed narrowing of the descending thoracic aorta approximately 2 cm. distal to the origin of the left subclavian artery (Figs. 1 and 2). The stenotic segment appeared to be 5 mm. in length. The innominate artery was tortuous and markedly dilated. The thyrocervical arterial trunk was elongated and dilated.

On Sept. 21, 1955, a left thoracotomy was performed. The intercostal arteries were only slightly enlarged. The coarctation was located at the level of the ligamentum arteriosum. The coarctated segment was excised and a primary end-to-end anastomosis was performed. The lumen of the stenotic segment measured 3 mm.

The postoperative course was essentially uneventful. The blood pressure in the arms remained at 110 to 140 mm. Hg systolic and 70 to 90 mm. Hg diastolic. When the patient was first allowed out of bed on the eighth postoperative day, she promptly fainted as hypotension recurred. The tight-fitting corset was again used to control the hypotension. The amount of compression required to prevent postural attacks decreased progressively, and she was discharged on the twentieth hospital day in excellent condition.

Six weeks following the operation the patient was able to abandon the corset, and has been free of postural symptoms ever since. At the present time she is completely well and working full time. The suprasternal mass is only slightly apparent. The blood pressure in the arms continues in the range of 110 to 140 mm. Hg systolic and 70 to 80 mm. Hg diastolic, and is slightly higher in the legs. The suprascapular pulsations and bruit have disappeared. The soft systolic murmur is still heard along the left sternal border. The femoral arterial pulsations are full and no longer delayed. The roentgenogram shows that the heart is now normal in size; the aortic knob is unchanged.

COMMENT

In discussing this patient's problem preoperatively it was agreed that correction of the coarctation seemed to be indicated. However, it was not at all clear whether the postural hypotension would be helped or aggravated by the procedure. The gradual loss of the long-standing, crippling syncope following operation was gratifying but difficult to understand. It is possible that the reduction in the arterial pressure gradient of blood flow from the upper to the lower parts of the body was contributory, the postural "run-off" being less sudden and less severe. That this is not the entire explanation is borne out by the recurrence of syncope in the immediate postoperative period when the blood pressure in the arms was essentially normal. The loss of the postural symptoms over a 6-week period suggests a gradual return of sympathetic tone in the splanchnic vascular bed. It is impossible to say how, or whether, this was related to resection of the coarctation.

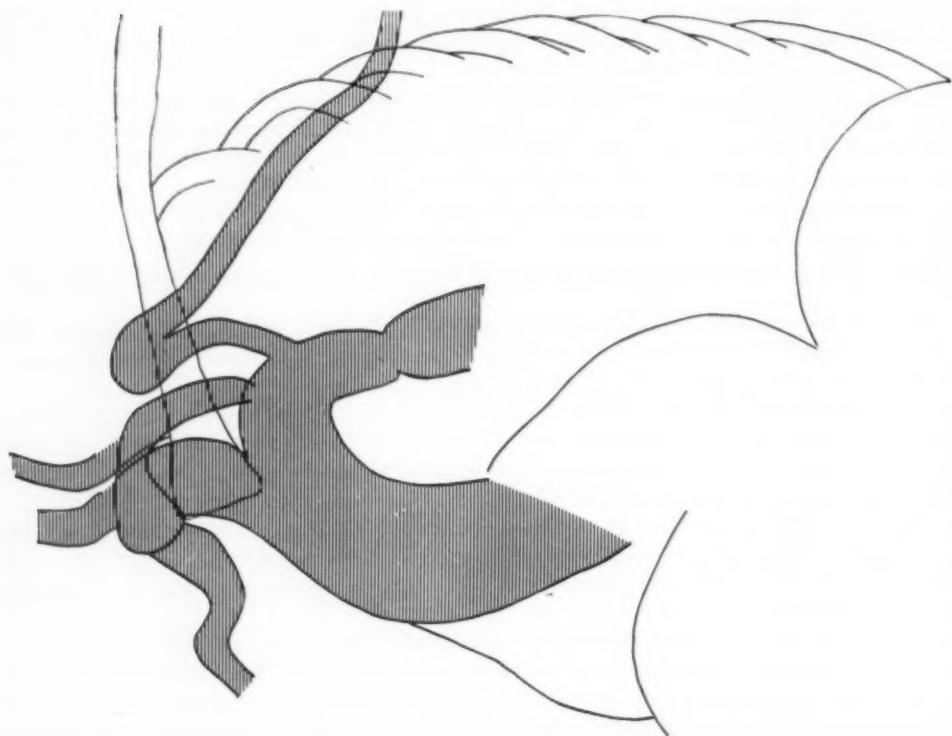


Fig. 1.—Angiocardiogram in the right posterior oblique view.



Fig. 2.—Diagram of the angiogram of Fig. 1.

To our knowledge, the occurrence of hypotension in a setting such as that provided by our patient has not been reported previously in the medical literature. Glenn and associates³ reported a patient with coarctation involving the distal thoracic aorta and the celiac axis. Bilateral dorsal sympathectomy, performed 4 years earlier, had not influenced the hypertension but postural hypotension did not develop. Following resection of the coarctation and anastomosis of the splenic artery to the proximal aorta, the blood pressure fell to the normal range. In a review by Reifenstein and co-workers,⁴ of 104 autopsied cases of coarctation of the aorta, mention is made of a few patients who had bilateral sympathectomy for hypertension. The follow-up was not discussed and reference to postural hypotension was not made.

The lack of rib-notching in the roentgenograms of the chest in an adult is unusual. Reifenstein and associates,⁴ however, reported absence of rib-notching in 25 per cent of their series. The enlarged thyrocervical trunk was atypical and probably served as the main proximal collateral channel, thus accounting for the absence of notching of the ribs.

The pulsating mass in the suprasternal notch was confirmed by the angiogram to be a buckled innominate artery. Sir John Parkinson and co-workers⁵ have emphasized that such a mass, in a young adult with hypertension, is strong presumptive evidence for coarctation of the aorta. With subsidence of the hypertension the swelling has almost disappeared.

SUMMARY

A patient with coarctation of the aorta is reported, in whom dorsal sympathectomy, 10 years earlier, left the arterial hypertension unchanged and caused severe postural hypotension. Both hypertension and postural hypotension were corrected by operative removal of the coarctation.

REFERENCES

1. Gross, R. E., and Hufnagel, C. A.: Coarctation of the Aorta: Experimental Studies Regarding Its Surgical Correction, *New England J. Med.* **233**:287, 1945.
2. Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment, *J. Thoracic Surg.* **14**:347, 1945.
3. Glenn, F., Keefer, E. B., Speer, D. C., and Dotter, C. T.: Coarctation of the Lower Thoracic and Abdominal Aorta Immediately Proximal to the Celiac Axis, *Surg. Gynec. & Obst.* **94**:561, 1952.
4. Reifenstein, C. H., Levine, S. A., and Gross, R. D.: Coarctation of Aorta: A Review of 104 Autopsied Cases of The Adult Type, *AM. HEART J.* **33**:146, 1947.
5. Parkinson, J., Bedford, D. E., and Almonds, S.: The Kinked Carotid Artery That Simulates Aneurysm, *Brit. Heart J.* **1**:345, 1949.

Review

The Atrial Complex of the Electrocardiogram

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At present the electrocardiogram has a wide range of uses in clinical medicine. These extend from the diagnosis of myocardial infarction to the detection of nonspecific abnormalities which cannot be recognized by other methods of examination and include, among others, the identification of arrhythmias, localized chamber enlargement, and electrolyte disorders. This status of electrocardiography is the result of extensive clinical and experimental observation, and it is likely that future work will extend both the range and precision of electrocardiographic diagnosis.

One area in which electrocardiography is almost certain to be improved is that of detecting atrial abnormalities. The data on which clinical use of the electrocardiogram is now based concern mainly the form of the ventricular complex and the temporal relations of atrial and ventricular activity. It is probable that additional diagnostically useful information concerning the size and state of the atrial muscle may be obtained from detailed study of the atrial complex. Such information would be of special import, since the recognition of atrial abnormalities by other techniques has serious limitations.

As a basis for future studies directed at improving the diagnosis of atrial abnormalities by electrocardiographic methods it is appropriate to review some of the available information concerning (1) factors which influence the atrial complex, (2) known electrocardiographic effects of atrial abnormalities, and (3) special techniques and analyses which have been applied to the detection of atrial abnormalities by electrocardiographic methods. It is also appropriate to review the limitations of present information in these areas and to examine methods by which this information may be supplemented. The present review will concern mainly the anatomic atrial abnormalities and their detection by electrocardiographic techniques. The atrial arrhythmias which constitute a special group of functional abnormalities will not be considered.

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FACTORS WHICH INFLUENCE THE ATRIAL COMPLEX

The factors which affect the atrial complex are similar to those which influence the more extensively studied ventricular complex. They include the nature of electrical phenomena in the cells of the atria, the pattern and rapidity of atrial excitation and recovery, the size, shape and anatomic position of the atria, the electrical properties of the body, and the type of electrode system and recording employed. Not all of these factors will be described in detail in this review, but selected examples of their influence on the atrial complex will be given and some of the shortcomings of present information will be cited.

Cellular Phenomena.—The nature of the cellular processes involved in cardiac excitation and recovery is under intensive study, and the information obtained will undoubtedly contribute to more precise use of the electrocardiogram in clinical problems. The present state of knowledge in this extensive field cannot be reviewed here, but examples of the manner in which knowledge of individual cell processes may influence the interpretation of the gross form of the atrial complex can be outlined. As indicated by Macleod's classic analysis, the process of recovery in the atria begins prior to completion of atrial excitation.¹ A portion of the atrial complex thus represents the combined effects of both processes. Alteration in the duration of the cellular action potential would be expected to change the form of the atrial complex by affecting the temporal relation of excitation and recovery. Vagal stimulation which decreases the duration of the atrial action potential might be expected to decrease the amplitude of some portions of the atrial complex, since recovery of some cells would then be superimposed on the effects of excitation at an earlier time. This mechanism may be involved in the effect of heart rate on P-wave amplitude, with slow rates being associated with small amplitude of the P waves.

There are many other possible applications of information from basic cellular studies to the analysis of clinical electrocardiograms. Brooks and co-workers² have demonstrated that a unipolar electrocardiogram from a site adjacent to that of an intracellular microelectrode shows the rapid positive-negative intrinsic deflection of the electrocardiogram to be simultaneous with the upstroke of the transmembrane potential record. When the electrocardiogram and the intracellular potential are recorded from more widely separated sites, the intrinsic deflection and the upstroke of the action potential are no longer synchronous. These findings were true of both atrial and ventricular muscle and constitute a direct demonstration of the fact that the intrinsic deflection signals the occurrence of excitation at a unipolar electrode site. These examples of the application of information from cellular studies to the analysis of electrocardiograms are intended to illustrate an approach which is almost certain to lead to more rational use of the records in clinical situations.

The Sequence of Atrial Excitation and Recovery.—It is obvious that the time course of activation and recovery is one of the major factors determining the form of the atrial complex. The most widely accepted description of the sequence of atrial excitation is based on the work of Lewis, Meakins and White.³ From measurements of the intrinsic deflection at various points on the surface of dog atria, they concluded that atrial excitation spread radially from the pacemaker

with a conduction velocity of 600 to 1,200 mm. per second. This description has been questioned by several other workers. Eyster and Meek⁴⁻⁶ repeatedly reported evidence for more rapid spread of excitation from the sinus node to the atrioventricular node than occurred in other portions of the atria. Bachmann⁷ reported evidence for a preferential conduction route from right to left atrium over a posterior interatrial band. His findings indicated that crushing this band delayed the time difference between right and left auricular contraction by 3 to 4.6 times the normal average. He later reported a case in which the electrocardiogram showed deep notching of the P wave, and pathologic alterations of the interatrial band were demonstrated at autopsy.⁸ In a more recent study, Puech and associates⁹ found the most rapid spread of atrial excitation in the region between superior and inferior venae cavae and in the interatrial bridge. These workers also reported that the latest portion of the atrium to undergo excitation was the region of the left inferior pulmonary vein rather than the tip of the left atrial appendage as is commonly supposed. They reported conduction rates in the right atrial body ranging from 487 to 1,100 mm. per second.

In view of the differences in the mode of atrial excitation reported to date, and particularly in view of all of the evidence which conflicts with the common concept of simple radial excitation, further studies of the excitation sequence would be desirable. For this purpose, instrumentation similar to that employed by Scher¹⁰ and by Durrer¹¹ and their co-workers to investigate the sequence of ventricular excitation would be most appropriate.

Whatever the pattern by which atrial excitation advances, it is apparent that the exact locus of the pacemaker will influence the form of the atrial complex. Anatomic observations indicating the human sinoatrial node to be a more extensive structure than was formerly believed has been reported by Davies.¹² According to his findings the sinoatrial node is horseshoe-shaped and embraces the ventral aspect of the end of the superior vena caval ring, with the anterior limb extending caudally over more than the upper half of the sulcus terminalis. If any portion of this structure can operate as the normal pacemaker, considerable variation in the mode of atrial activation, and thus in the form and apparent duration of the atrial complex, could exist within the boundaries of normal sinus rhythm. This constitutes one of the many reasons why the range of normal variations of the atrial complex must be adequately described in order to serve as a basis for recognizing abnormalities.

The recovery process in the atria presents special problems for study, since the resulting electrocardiographic deflection is largely obscured by the ventricular complex. In instances of complete heart block it has been noted that the atrial recovery wave (T_p) is of opposite polarity to the P wave, and there is evidence that the area of these waves is related. Gross¹³ reported that displacement of the P-R segment representing the early portion of the T_p wave increased with increasing cardiac rates, and that the amount of displacement correlated directly with the area of the P wave. Attempts have been made to assess the area of P and T_p waves and to employ these values to calculate the atrial gradient. Berkun and associates¹⁴ recorded three simultaneous leads at a paper speed of

50 mm. per second and a standardization of 1 mv. per 15 mm. of deflection, on patients with complete A-V block, for this purpose. Results indicated a gradient close to zero, suggesting that the time course of atrial recovery is close to that of atrial excitation. Littman and associates¹⁵ reported that isopropylarterenol in normal young adults produced tachycardia and slightly increased amplitude of P waves, but a greater augmentation of the T_p wave and thus a change in the atrial gradient as evaluated qualitatively from the conventional limb leads. There are local variations in the duration of the excited state of the atria, as indicated by the work of Alessi and associates.¹⁶ In the absence of vagal stimulation the refractory period at various points on the dog atrium was found to vary by as much as 40 milliseconds, and with vagal stimulation the refractory period of some points was unaffected while that of other points decreased as much as 140 milliseconds. Since the refractory period is almost certainly closely related to the duration of the excited state, these studies indicate rather wide variations in different portions of the atria. These studies concerned small areas on the atrial surface and probably represent variations in response of these areas related to their proximity to vagal endings. Since the vagal endings seemed to be irregularly distributed, it is still possible that the over-all pattern of atrial recovery may be similar to that of excitation.

At the present time it is extremely important in electrocardiographic interpretation to be aware of the possibility that S-T segment displacement may be the result of the superimposed atrial recovery wave. Estimates of the significance of S-T segment and S-T junction displacements should take into account the approximate area of the P wave in the lead under consideration. When the P-wave area is large, present information suggests that the T_p area is also likely to be large and that S-T segment and junction displacement may be at least partially the result of this wave. To partially obviate this difficulty in electrocardiographic interpretation, it has been suggested that the level of the S-T junction be measured with reference to the level of the P-R rather than the T_p segment of the tracing.¹⁷

Atrial Size, Shape, and Position Within the Thorax.—These factors together with the point of origin of excitation and the excitation and recovery sequence are obviously important factors determining the form of the atrial complex. The relation of all of these to the form of the atrial complex has been investigated with coplanar outlines of the dissected atria and with casts of the atrial cavities.¹⁸⁻²⁰ In these studies a radial excitation pattern was inscribed on the outlines or casts and employed to derive the form of P waves in various electrocardiographic leads and PsE loops of the vectorcardiogram in various planes. The results provided several insights into the relation of excitation sequence, pacemaker site, and atrial size, shape and position to the form of the atrial complex. It was apparent that high, peaked P waves in Leads II, III, and V_F were the expected results of right atrial enlargement, and wide, notched waves in Lead I were to be expected with left atrial enlargement. These findings were the result of atrial shape and were not dependent on an altered sequence of excitation or on an unusual atrial position. It was also possible to estimate the degree of P-wave prolongation to be expected with various degrees of atrial enlargement

and to describe the approximate form of P waves resulting from ectopic excitation initiated at several different sites. Various modifications of this approach appear appropriate for further studies of the effect of certain normal variables, such as atrial position, and the effect of abnormalities, such as localized atrial lesions, on the form of the atrial complex.

Conducting Medium, Electrode Systems, and Type of Recording.—One of the most active areas of electrocardiographic research has been that of devising electrode systems which do not necessitate the assumption that the body be represented by a simple geometric figure.²¹⁻²⁶ None of the recently proposed lead systems has been extensively employed in clinical studies, but the possibility exists that they may provide useful information concerning the state of the atria as well as that of the ventricles. In particular, the antero-posterior component of atrial electrical activity may furnish such information. In one study with the Frank electrode system it was found that in the majority of normal records the maximal atrial vector was directed forward, while in a small number of records from patients with left atrial enlargement this vector was directed posteriorly.²⁷ Pipberger²⁸ studied the P-wave duration and P-R interval in electrocardiographic leads recorded with the Schmitt SVEC-III electrode system and reported values which differed from generally accepted normal limits for conventional leads. These values will be useful as a basis for investigating the effect of atrial abnormalities on the atrial complex recorded with orthogonal electrode systems.

The heart's electrical activity may be recorded in many different forms, and some of the displays may provide information other than that furnished by the conventional electrocardiogram. This possibility applies to the recognition of atrial as well as ventricular abnormalities. The vectorcardiogram is one of the possible displays of cardiac electrical events and has the merit of combining data from more than one lead axis simultaneously.²⁹ Whatever displays of atrial activity are employed in future studies, there is a need for greater amplification, more adequate representation of time, and probably for greater fidelity than is provided by conventional electrocardiographs. In electrocardiograms recorded at a paper speed of 25 mm. per second and with a standardization of 10 mm. per millivolt, the average normal P wave in Lead II has a maximal amplitude of 1 mm. and a duration of 2.25 mm.³⁰ Since it is difficult to recognize variations of either voltage or time represented by less than 0.5 mm., the P wave must be increased in maximal amplitude by 50 per cent in order to constitute a recognizable change. In the previously referred to study of atrial enlargement by means of casts, such increases in maximal amplitude were only reached with 80 per cent enlargement of the linear dimensions of the right atrium.²⁰ To be recognized in the conventional electrocardiogram, the P-wave duration would need to be increased by 20 per cent, and in the study mentioned such degrees of prolongation occurred only with 20 per cent or more enlargement of the linear dimensions of either atrium.

ELECTROCARDIOGRAPHIC EFFECTS OF ATRIAL ABNORMALITIES

In routine electrocardiographic interpretation the duration, maximal amplitude, and general contour of the P waves are observed. Criteria of normal and

tables of normal limits for amplitude and duration of this wave for various ages, heart rates, and specific leads are available.^{17,30-35} High, peaked waves in Leads II, III, and V_F and wide, notched waves in the standard and unipolar limb leads are the major abnormalities of form which are noted in the presence of sinus rhythm. In a few instances atrial infarction has been recognized by elevation of the P-T_p segment.³⁶⁻⁴⁰ The incidence of atrial infarction at autopsy has been investigated by Cushing and associates,⁴¹ who reported the atria to be involved in 17 per cent of a series of 182 cases of myocardial infarction. Bean,⁴² however, observed atrial involvement in only 3 of 300 hearts with myocardial infarction, and Wartman and Hellerstein⁴³ found a 7 per cent incidence of atrial infarction in 132 infarcted hearts. Several authors have emphasized the frequent occurrence of atrial dysrhythmias in patients with atrial infarction. Abramson and associates⁴⁴ studied the electrocardiographic effects of experimental injury to the auricular myocardium and found elevation of the P-T_p segment in various leads, depending on the site of the injury. Sanders⁴⁵ also studied experimental localized auricular necrosis and reported frequent alterations of the P-T_p segment. James and Geoghegan⁴⁶ produced experimental auricular injury by injection of air into the ventricular cavity and described the sequential alterations of direct auricular leads. These began with displaced P-T_p segments and evolved into tracings with a sharp auricular recovery wave.

The most frequent abnormalities of the P waves by current standards occur in the presence of heart disease and usually reflect fairly marked degrees of atrial enlargement. Criteria which would permit recognition of less marked degrees of enlargement would obviously be desirable. It is common knowledge that right atrial enlargement is often associated with tall, sharply pointed P waves which are usually most evident in Leads II, III, and V_F, and that left atrial enlargement often results in wide, notched P waves in one or more of the standard leads. There are, however, frequent apparent exceptions to these generalities, and tall P waves occur in a number of patients with mitral valvular lesions in whom left atrial enlargement may be expected. Gibert-Queraltó and associates⁴⁷ reported that the "mitral P wave" with increased duration and notching or a flat top, without increased amplitude, occurred in only 30 per cent of a series of patients with mitral stenosis. Increased amplitude simulating "pulmonary P waves" was frequent in these patients, and, in general, appeared in those with pulmonary hypertension. These authors reported decreased amplitude of the P waves in relation to the reduction of pulmonary hypertension after mitral commissurotomy. Lewis and associates⁴⁸ reported, however, that the incidence of moderate or marked left atrial enlargement was approximately the same in patients with mitral stenosis with and without abnormal P waves. They also reported that elevations of pulmonary arteriolar resistance were comparable in patients with and without abnormal P waves. They did find a greater incidence of right ventricular enlargement in patients with mitral stenosis and abnormal P waves than in those with normal P waves. In their opinion the relationship of abnormal P waves to the severity of stenosis and the degree of pulmonary arteriolar obstruction was ambiguous. In an extensive study of normal and abnormal P waves, Thomas and DeJong⁴⁹ concluded that right atrial abnormality

could be recognized by P waves in Lead CR₁ which were more than 2.5 mm. in amplitude and diphasic, pointed or bifid, with the first peak having the greater amplitude. In their study, left atrial abnormality was manifest by P waves in Leads CR₄ or CR₇ that were more than 3 mm. in amplitude and bifid, with the second peak being larger, or by an abnormally long interval between the peaks of a bifid wave in any lead. Combined atrial enlargement was suggested by a combination of these findings. These authors also found evidence of right atrial abnormality in a third of their patients with mitral stenosis, and moderate symptoms in half of the more severe cases and those with cardiac enlargement. They state that the ECG evidences of right atrial abnormality were most marked in the cases with clinical evidence of pulmonary hypertension. Wood⁵⁰ found tall, sharp P waves to be the most significant electrocardiographic abnormality in cases of chronic pulmonary heart disease and reported their occurrence in 85 of 100 cases. He also reported an association between this finding and elevated right ventricular pressure. Fox and Kremer,⁵¹ however, studied the atrial complex in the electrocardiograms of patients with pulmonary tuberculosis and concluded that P-wave abnormalities could not serve as a criterion for the existence of *cor pulmonale*.

It is apparent that altered size and shape of the atria are factors in producing the abnormal P waves associated with atrial enlargement. It has also been suspected that decreased conduction velocity of the excitation process may be a factor in P-wave prolongation with atrial disease. Deeply notched P waves of greater than normal duration attributed to defective intra-auricular conduction have been reported by Feiring⁵² and by Decherd and associates.⁵³ In Sanders' experimental study of localized atrial necrosis he reported that in 2 out of 37 instances intra-auricular block manifested by unusually tall, broad, slurred, and notched auricular complexes occurred.⁴⁶ At present the possible role of localized atrial lesions in the production of increased P-wave duration is not clear. Further experimental study of the effect of localized and generalized atrial disease on the conduction velocity and excitation pattern would be extremely pertinent to the aim of improving electrocardiographic diagnosis of atrial abnormalities.

Of major importance for future studies directed at improving the diagnosis of atrial abnormalities is a detailed description of the range of variation of normal atrial complexes. This applies not only to the range of variation encountered in large numbers of normal records but also to the range in records from single individuals on different occasions and under different circumstances. Definition of the latter range and the factors responsible for it would permit more rational use of the serial records of individual subjects for the identification of abnormal atria. Gross⁵⁴ studied the influence of rate on the shape of the P wave in Lead II and reported that low rates favor a peaked or notched shape, while high rates usually occur with a rounded shape of the wave. Lepeschkin⁵¹ states that the duration of the P wave decreases with increasing cardiac rates, and Kesselman and associates⁵⁵ found decreased duration of the entire atrial complex with increased atrial rates in patients with complete heart block. Ashman and Hull⁵⁰ also state that the duration of the P wave varies inversely with the heart rate. Scherf⁵⁶ reported periodic changes in the form of the P waves in association with

partial heart block and suggested that variations in vagal tone influenced the site of impulse formation or their pattern of spread over the atria. Further and more detailed description of the normal variations of the atrial complex would be an important step toward improved recognition of atrial abnormalities.

SPECIAL TECHNIQUES AND ANALYSES APPLIED TO THE DETECTION OF ATRIAL ABNORMALITIES

A variety of recordings other than conventional electrocardiograms, and analyses other than those routinely employed in electrocardiographic interpretation have been investigated in attempts to improve the recognition of atrial abnormalities. Langer⁵⁷ recorded high-fidelity, high-gain electrocardiograms with a time scale of 330 mm. per second from the cathode-ray oscilloscope. He reported that P waves have a much more complex wave form than is apparent in conventional electrocardiograms and suggests that the method may be useful for the study of auricular excitation. Systematic investigation of the range of normal variation of atrial complexes recorded in this manner and of the effects of atrial abnormalities have not yet been carried out, but such records may well provide useful diagnostic information in excess of that furnished by the ordinary electrocardiogram.

The PsE loop of the spatial vectorcardiogram recorded with several electrode systems has been described for normal subjects and for small numbers of patients with atrial abnormalities.⁵⁸⁻⁶² Sano and co-workers⁶³ reported normal PsE loops to be small, closed or only slightly open, and directed almost entirely downward. The loop of left atrial enlargement was larger and more open and the maximal vector was directed posteriorly, inferiorly, and to the left. That of right atrial enlargement was largest and most widely opened and was directed anteriorly and downward. The authors concluded that the PsE loop was often helpful clinically in the differentiation between right and left atrial enlargement when standard electrocardiograms were equivocal. At present, vectorcardiographic studies of the atrial complex are not numerous enough to prove or disprove the usefulness of the technique in identifying atrial abnormalities. As is true of other electrical events in the heart, the simultaneous effects of these events on more than one lead axis may provide useful information other than that furnished by the electrocardiogram. Further studies of the atrial vectorcardiogram are certainly in order.

Esophageal electrodes provide a method of obtaining "semidirect" atrial leads.⁶⁴ The major use of such leads to date has been in the identification of the cardiac mechanism, but it is probable that they may also be useful in the recognition of anatomic abnormalities of the atria.⁶⁵⁻⁶⁷ Oblath and Karpman⁶⁸ have described the form of the normal esophageal electrocardiogram and reported in tabular form the variations in amplitude and duration of the various components. Hecht and Woodbury⁶⁹ recorded direct electrocardiograms from human auricular muscle *in situ* and concluded that their form could be explained as the effects of a moving dipole on the electrode. They applied this concept to semi-direct esophageal leads and concluded that the intrinsicoid deflection in these

leads could be employed to estimate left auricular hypertrophy. They further concluded that a broad, bifid P wave in Lead I and sharply diphasic P waves in Lead V₁ could be considered to result from left auricular enlargement. The second hump of the P wave in standard leads and the negative trough in Lead V₁ were found to coincide with the onset of the intrinsicoid deflection in esophageal leads. They felt, however, that right auricular hypertrophy could not be diagnosed from the electrocardiogram because there is no semidirect thoracic lead reflecting the changes of the right atrium. In studying patients with tall, upright P waves in Leads II and III they found that esophageal leads did not show late activation of the left auricle, and therefore postulated that such P waves are not caused by unilateral auricular hypertrophy but may be primarily the result of abnormal cardiac rotation or of dilatation.

One of the major difficulties in the use of esophageal electrodes has been the technical one of a shifting base line, which is produced mainly by variations in the contact of electrode and esophageal wall. This difficulty can be largely overcome with the use of a simple saline-bridge electrode described by Brody.⁷⁰ Brody and Copeland⁷¹ have also employed advanced electrocardiographic concepts, including that of the lead field, to develop a group of laws relating the form and magnitude of esophageal electrocardiograms to the electromotive forces of the heart. These steps of improving the technique and providing a sound theoretical basis for the interpretation of the esophageal electrocardiogram are important advances and may contribute significantly to improved recognition of atrial abnormalities.

Macruz and co-workers⁷² have suggested an interesting technique of analysis aimed at improving the diagnosis of atrial enlargement from the conventional electrocardiogram. Their analysis is based on the temporal relations of various events within the P-R interval of the electrocardiogram. The beginning of the P wave represents the onset of excitation in the right atrium and is followed successively by the onset of excitation in the left atrium, activation of the A-V node, and completion of excitation in the right atrium, all occurring at indeterminate points during the inscription of the P wave. Completion of left atrial excitation occurs at the end of the normal P wave. The authors reasoned that left atrial enlargement would not prolong the time necessary for excitation to reach the A-V node, but would prolong the total duration of the P wave itself. Thus, the P-R segment would be shortened and the P-wave duration increased, while the P-R interval would be unchanged. Right atrial enlargement, on the other hand, would be expected to prolong the interval between the onset of right atrial excitation and delivery of activation to the A-V node. According to the authors, the P-wave duration would be unaffected unless the enlargement were sufficient to make terminal excitation of the right atrium later than that of the left atrium. Thus, right atrial enlargement would be expected to prolong the P-R interval and alter the P-wave configuration but not usually affect the P-wave duration. The authors propose the ratio of P-wave duration to P-R segment duration as an index of atrial enlargement, and from clinical data reported they suggest that a ratio of less than 1 indicates right atrial enlargement and a ratio greater than 1.6 suggests left atrial enlargement. In the theoretical analysis presented the au-

thors do not take into account the possibility that left atrial excitation may have a later than normal onset in the presence of right atrial enlargement, because of the increased mass of right atrium which must be traversed prior to left atrial excitation. P-wave prolongation might thus be produced by right atrial enlargement even though left atrial activation is the terminal event during the P wave. The major point of the analysis, however, is that left atrial enlargement would be expected to shorten the P-R segment while right atrial enlargement would not, and this point still appears to be valid, since not only the onset of left atrial excitation but the time of A-V nodal excitation would be expected to be delayed in right atrial enlargement. The proposed ratio appears to deserve widespread clinical application in order to determine its merit as an index of atrial enlargement.

SUMMARY

Current use of the electrocardiogram in the recognition of atrial abnormalities is based on increased duration and/or amplitude of the P waves and on gross abnormalities of form, such as pronounced notching, or the rare occurrence of P-T_p segment elevation with atrial infarction. These abnormalities are usually the result of severe atrial pathology, and it is likely that less marked abnormalities may be recognized and more precisely differentiated by electrocardiographic methods. Several types of studies are appropriate to achieve this aim. More detailed knowledge of the sequence and conduction velocity of electrical events in normal and diseased atria would be very desirable. Such information could be employed to derive the expected form of the normal atrial complex in ECG leads or other displays of atrial activity and to predict the effect of various lesions. Recording equipment with expanded time scale and higher gain and fidelity than current electrocardiographs is desirable for the study of electrical events in the atria. Recordings other than conventional electrocardiograms may provide certain items of useful information which cannot be extracted from ECG leads. Remote-lead systems which include a projection of electrical activity on an antero-posterior axis, and critical study of P waves in esophageal leads may contribute to improved recognition of atrial abnormalities. Clinical studies in which the range of normal variation is defined, not only for amplitude and duration but also for detailed form of the P waves, PsE loops, or other records of atrial activity, will be necessary. Finally, detailed description of the atrial complex in various specific abnormalities must be carried out and the presence of the lesions confirmed at autopsy. These are the same general steps by which useful information concerning the ventricular complex has been and is continuing to be obtained. It is likely that the same approach applied to the atrial complex will result in improved criteria for the electrocardiographic recognition of atrial abnormalities.

REFERENCES

1. Macleod, A. G.: *AM. HEART J.* **15**:165, 1938.
2. Brooks, C. McC., Hoffman, B. F., Suckling, E. E., and Orias, O.: *Excitability of the Heart*, New York, 1955, Grune & Stratton, Inc.

3. Lewis, T., Meakins, J., and White, P. D.: Phil. Trans. Roy. Soc. **205**:375, 1914.
4. Eyster, J. A. E., and Meek, W. J.: Heart **5**:119, 1913-14.
5. Eyster, J. A. E., and Meek, W. J.: Arch. Int. Med. **18**:775, 1916.
6. Eyster, J. A. E., and Meek, W. J.: Am. J. Physiol. **61**:130, 1922.
7. Bachmann, G.: Am. J. Physiol. **41**:309, 1916.
8. Bachmann, G.: Ann. Int. Med. **14**:1702, 1941.
9. Puech, P., Esclavissat, M., Sodi-Pallares, D., and Cisneros, F.: AM. HEART J. **47**:174, 1954.
10. Scher, A. M., Young, A. C., Malmgren, A. L., and Paton, R. P.: Circulation Res. **1**:539, 1953.
11. Durrer, D., and van der Tweel, L. H.: AM. HEART J. **46**:683, 1953.
12. Davies, F.: Brit. Heart J. **4**:66, 1942.
13. Gross, D.: AM. HEART J. **50**:24, 1955.
14. Berkun, M. A., Kesselman, R. H., Donoso, E., and Grishman, A.: AM. HEART J. **52**:858, 1956.
15. Littman, A., Grossman, M. I., Gunnar, R. M., Isaacs, J. H., Hirschmann, J. H., and Foley, E. F.: J. Appl. Physiol. **3**:235, 1950.
16. Alessi, R., Nusynowitz, M., Abildskov, J. A., and Moe, G. K.: Am. J. Physiol. **194**:406, 1958.
17. Kossmann, C. E.: Circulation **8**:920, 1953.
18. Abildskov, J. A., Cronvich, J. A., and Burch, G. E.: Circulation **11**:97, 1955.
19. Abildskov, J. A., Barnes, T. G., and Hisey, B. L.: AM. HEART J. **52**:496, 1956.
20. Abildskov, J. A.: AM. HEART J. **53**:55, 1957.
21. Frank, E.: Circulation **13**:737, 1956.
22. Helm, R. A.: AM. HEART J. **53**:415, 1957.
23. Schmitt, O. H., and Simonson, E.: A.M.A. Arch. Int. Med. **96**:574, 1955.
24. McFee, R., and Johnston, F. D.: Circulation **8**:554, 1953.
25. McFee, R., and Johnston, F. D.: Circulation **9**:255, 1954.
26. McFee, R., and Johnston, F. D.: Circulation **9**:868, 1954.
27. Abildskov, J. A., Street, W. W., Solomon, N., and Toomajian, A. H.: Circulation **17**:1069, 1958.
28. Pipberger, H. V., and Tanenbaum, H. L.: Circulation **18**:1175, 1958.
29. Cronvich, J. A., Burch, G. E., and Abildskov, J. A.: Circulation **8**:914, 1953.
30. Ashman, R., and Hull, E.: Essentials of Electrocardiography, New York, 1945, The Macmillan Company.
31. Lepeschkin, E.: Modern Electrocardiography, Baltimore, 1951, Williams & Wilkins Company.
32. Wolff, L.: Electrocardiography, Philadelphia, 1956, W. B. Saunders Company.
33. White, P. D., and Bock, A. V.: Am. J. M. Sc. **156**:17, 1918.
34. Alexander, A. A., Knight, H. F., and White, P. D.: Arch. Int. Med. **36**:712, 1925.
35. White, B. V., Parker, R. C., and Master, A. M.: Arch. Int. Med. **74**:94, 1944.
36. Hellerstein, H. K.: AM. HEART J. **36**:422, 1948.
37. Wilson, J. L., and Knudson, K. P.: New England J. Med. **251**:559, 1954.
38. Miller, R., and Perelman, J. S.: AM. HEART J. **31**:501, 1946.
39. Graef, I.: Bull. U. S. Army M. Dept. **8**:481, 1948.
40. Young, E. W., and Koenig, A.: AM. HEART J. **28**:287, 1944.
41. Cushing, E. H., Feil, H., Stanton, E. J., and Wartman, W. B.: Brit. Heart J. **4**:17, 1942.
42. Bean, W. B.: Ann. Int. Med. **12**:71, 1938.
43. Wartman, W. B., and Hellerstein, H. K.: Ann. Int. Med. **28**:41, 1948.
44. Abramson, D. I., Fenichel, N. M., and Shookhoff, C.: AM. HEART J. **15**:471, 1938.
45. Sanders, A.: Am. J. M. Sc. **198**:690, 1939.
46. James, T. N., and Geoghegan, T.: AM. HEART J. **46**:830, 1953.
47. Gibert-Queraltó, J., Torner-Soler, M., and Balaguer-Vintró, I.: AM. HEART J. **49**:548, 1955.
48. Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: AM. HEART J. **43**:2, 1952.
49. Thomas, P., and Dejong, D.: Brit. Heart J. **16**:241, 1954.
50. Wood, P.: Brit. Heart J. **10**:87, 1948.
51. Fox, T. T., and Kremer, H. S.: Am. Rev. Tuberc. **47**:135, 1943.
52. Feiring, W.: AM. HEART J. **39**:773, 1950.
53. Decherd, G. M., Ruskin, A., and Brindley, P.: AM. HEART J. **31**:352, 1946.
54. Gross, D.: AM. HEART J. **51**:880, 1956.
55. Kesselman, R. H., Berkun, M. A., Donoso, E., and Grishman, A.: AM. HEART J. **51**:900, 1956.
56. Scherf, D.: AM. HEART J. **29**:213, 1945.
57. Langer, P. H.: Circulation **5**:249, 1952.
58. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.
59. Conway, J. P., Cronvich, J. A., and Burch, G. E.: AM. HEART J. **38**:537, 1949.
60. Briller, S. A., Marchand, N., and Korrman, C. E.: Rev. Sc. Instruments **21**:805, 1950.
61. Burch, G. E., Abildskov, J. A., and Cronvich, J. A.: Circulation **7**:558, 1953.

62. Fowler, N. O., and Corney, E. R.: AM. HEART J. **48**:36, 1954.
63. Sano, T., Hellerstein, H. K., and Vayda, E.: AM. HEART J. **53**:854, 1957.
64. Brown, W. H.: AM. HEART J. **12**:1, 1936.
65. Enselberg, C. D.: AM. HEART J. **41**:382, 1951.
66. Bain, C. W. C.: Brit. Heart J. **13**:485, 1951.
67. Brown, W. H.: AM. HEART J. **12**:307, 1936.
68. Oblath, R., and Karpman, H.: AM. HEART J. **41**:369, 1951.
69. Hecht, H. H., and Woodbury, L. A.: Circulation **2**:37, 1950.
70. Brody, D. A., Harris, T. R., and Romans, W. E.: AM. HEART J. **50**:923, 1955.
71. Brody, D. A., and Copeland, G. D.: AM. HEART J. **57**:3, 1959.
72. Macruz, R., Perloff, J. K., and Case, R. B.: Circulation **17**:882, 1958.

Letter to the Editor

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FEBRUARY 21, 1959

To the Editor:

Your Editorial in the January issue was read with great interest, especially in regard to the inclusion in the Journal of "Letters to the Editor." Since provocative ideas for research are solicited, I herewith submit the following idea for a catheter, hoping that it will find critical judgment and a responsive manufacturer. The cardiac catheter which I propose is somewhat similar to the double way of Cournand, but it would embody two thermocouple electrodes at the distal ends. The near thermocouple should be at the proximal opening of the ordinary double way, while the other would simply be a woven extension without lumen but carrying the wires of the distal electrodes of the second thermocouple at a distance of 12 centimeters from the first. Thus, only 3 wires are needed, one being a neutral to serve the other two electrodes. The outfit is connected to a double-channel recording device capable of measuring minute differences in temperature (1/100th of one degree centigrade).

The idea is as follows: If a steady flow of a known volume of saline is injected in the catheter at a temperature registered by the first electrode, the differences in temperature in the second electrode will determine both the velocity and the dilution in the medium through which it has passed by simple calculation of mass heat gain or loss. Thus, the cardiac output and the individual stroke volume (3-channel recording against ECG) can be easily determined without recourse either to gas analysis or to dye estimation. The stroke volume has always been a bugbear among research workers, and this method seems to be a perfect answer to its individual estimation and variation under stress. The method can also be applied to calculate the flow in each lung separately. When the catheter is introduced into the aorta, the flow can be measured immediately, as well as the rate of flow to an organ by introducing the woven end into the feeding artery.

H. A. ZAKY

Book Reviews

RADIOISOTOPE IN DER HERZDIAGNOSTIK. By Hans Ludes, M.D., and Gerhard Lehnert, M.D., Jena, 1958, Gustav Fischer Verlag, 62 illustrations, 15 tables, 107 pages.

In their foreword, the authors raise the question as to whether a monograph in so recent a field as the application of isotopes in the diagnosis of heart disease might not be premature. While many of the applications are still in the experimental phase, this compact volume is timely and presents a well-written introduction to and review of this fast-developing and promising area. The book has been prepared on the basis of extensive experimental experience. One of the authors has also visited the important laboratories of isotope research in cardiovascular diseases in the United States. In spite of the small size of the volume, the review is quite comprehensive and the results of the authors are well integrated with other information.

In a short introduction the important question of technique, dosage, and radiation protection is discussed. The application of radioactive isotopes is divided into three basic phenomena: dilution (blood and cardiac volume), transport (partial cardiac and pulmonary circulation times), and accumulation or clearance of isotope concentration in the heart (coronary circulation). The various applications of isotopes are discussed after a brief historical review of other preceding and existing methods. The determination of coronary circulation is singled out by Knipping, in his foreword, as perhaps the most promising field for routine application in the near future.

It is unavoidable that important progress has been made since this volume went to press, including developments at the authors' own laboratory. This, however, does not detract from the value of the book, which is an excellent basis for following up recent developments.

HANDBOOK OF CARDIOLOGY FOR NURSES. By Walter Modell, M.D., F.A.C.P., Associate Professor, Cornell University Medical College; Attending Physician, New York Veterans Administration Hospital; Associate Attending Physician, Bellevue Hospital; and Doris R. Schwartz, B.S., R.N., Assistant Professor, Cornell University-New York Hospital School of Nursing; Public Health Nursing Coordinator, Comprehensive Care and Teaching Program, The New York Hospital-Cornell Medical Center. New York, 1958, Springer Publishing Company, Inc., 328 pages.

This book is composed of two main sections: the first is a simplified text on cardiology for the nurse, and the second is on the nursing care of the cardiac patient. From the point of view of the reviewer, a physician who cares for patients with heart disease, the section on cardiology is good, containing the sort of information necessary for the nurse who assists in the care of the patient, and, in addition, information which will help the nurse to understand the physician's purpose in carrying out various diagnostic and therapeutic measures. One would like to see more emphasis and encouragement directed toward the nurse in the use of her own powers of observation, for in many aspects of the care of the cardiac patient she has the best opportunity to

observe certain reactions and occurrences, especially transient ones. In the section on nursing care, all aspects of the care of cardiac patients are considered, including a chapter on the care of the patient undergoing cardiac surgery. Most physicians will like the admonition to spare the sick cardiac patient unnecessary observation and attention. A case history is used to illustrate how the nurse may function in the care of a family in which a responsible member is chronically ill with heart disease, and how she may make use of community resources in helping them.

One wishes that the authors had attempted to combine their talents in certain chapters, especially those relating to the sick cardiac patient. Many nurses would appreciate a well-chosen list of references to the medical literature.

YOU CAN INCREASE YOUR HEART-POWER. By Peter J. Steinrohn, M.D., F.A.C.P., Garden City, N. Y., 1958, Doubleday & Company, Inc., 381 pages.

This volume, intended for the patient with real or imaginary heart disease, is more likely to confuse than to enlighten. The author in his introduction modestly states: "In this book you will read (and learn) about many facets of heart diseases. I shall show you how to conserve and increase your heart-power. Whatever your complaint, REAL heart disease or IMAGINARY heart trouble, I guarantee that you will come away with as great an understanding of your heart as you will ever want to have. Somewhere in this book you will find the solution to your own heart problem, present or future." The egocentric, verbose tract that follows the introduction fails almost completely to fulfill the author's guarantee.

The central theme of the book is the notion that each of us in his lifetime (reckoned from the fourth week of gestation, when the heart begins to beat) has a total of about three and a half billion heartbeats allotted. When these are used up, life is necessarily at an end. It follows, although the author does not clearly say so, that longevity is directly related to pulse rate. He puts it this way: "If you are a spendthrift, if you carelessly throw away these precious beats as if their source were unending—you will run short of them much before you reach seventy. . . ." He adds a little later: "Whether you drive your heart at high speeds and recklessly is entirely up to you. That is why your heart's in your own hands."

To the extent that the theme is doggedly followed throughout the book, the author is quite logical. He assures us that "You can learn the art of relaxation," and that "exercise is bosh." Fatigue is said to drain off heart-power. Even the weather is indicted as an enemy of those who spend their heart-beat bank balance unwisely. "I think," we are told, "we should all take a daily peek at the barometer."

To this point, the author's ramblings are largely harmless, except insofar as they may lead patients, and possibly physicians, to accept almost total inactivity as prophylactically desirable. His dicta on anticoagulants, in spite of his careful indication that they may be dangerous, are questionable. The patient is assured that when the drugs are used properly, ". . . there is little to lose and much to gain." No mention of the extremely uncertain position of anticoagulants in cardiovascular therapy, and specifically in the treatment of myocardial infarction, is made. Similarly, the possibility that Dexedrine as used in the management of obesity may be hazardous is summarily dismissed. The end result of the chapter on obesity, which contains many sound recommendations, will almost certainly be to encourage patients to seek treatment of obesity by means of drugs and to reject more tedious dietary methods. Also on the debit side is the bland statement that ". . . many coronary patients might benefit from consultation with a qualified thoracic surgeon." The reference is to operations designed to promote revascularization of the ischemic myocardium, none of which has achieved wide acceptance. The patient, one must suppose, should not be permitted to know that unanimity of professional opinion on such matters has not been reached. And many a modern devotee of enlightened physical diagnosis will cringe when he reads: "As a diagnostic tool, most cardiologists would be lost without it [the ECG]. If I have to choose between that and my stethoscope, I would put my stethoscope in cold storage without hesitation."

Finally, this poorly organized and frequently misleading discourse does not begin to meet its avowed purpose. One gets the impression that it was dictated at high speed without benefit of outline or notes, that such of its message as is acceptable could easily be put in one tenth of

the space, and that the physician who recommends it for his cardiac patients should do so with caution. Although some good advice and valid information can be found scattered through its 381 pages, the over-all effect is most unfortunate. It is more likely to impose a barrier between the patient and his physician than to enhance the relationship. This is especially true if the physician does not accept Dr. Steincrohn's message en bloc.

An adequate notion of the book's impact and real purpose is provided by the author's final admonition: "Review your spending habits. Have you been profligate? Have you been throwing away your precious wealth to the four winds? Then take heed! Become miserly with your remaining heartbeats. Be jealous of your heart-power."

ELECTROCARDIOGRAPHY. By Michael Bernreiter, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Kansas Medical School; Chief of Electrocardiography, St. Mary's Hospital, Kansas City, Mo.; Fellow of the American College of Cardiology and Fellow of the American College of Chest Physicians. Philadelphia, 1958, J. B. Lippincott Company, 134 pages.

The author presents an outline of the commonly accepted bases used in the interpretation of electrocardiographic tracings, as well as samples of each of the common findings of electrocardiographic interest. However, the discussion of basic principles, such as depolarization and repolarization, is so sketchy and the use of common terms so inexact (e.g., *repolarization* is equated with *relaxation* of muscle), that the serious student will need to go immediately to other sources for clarification.

As to the practical technique of reading electrocardiograms, some objection may be made to the author's arbitrary decisions. For example, he defines first degree A-V block by a P-R interval above 0.20 second, without mention of rate or age. Several other specific objections could be offered.

This book cannot be recommended to the internist, the general practitioner, or the medical student.

Announcements

At the suggestion of Dr. Paul D. White, the INTERNATIONAL SOCIETY OF CARDIOLOGY FOUNDATION was initiated. This Foundation's aim is to encourage and finance scientific research within the scope of the International Society of Cardiology. We are indebted to Dr. White for having stimulated private generosity, which has already resulted in important donations.

The Committee of the Foundation includes: P. D. White, Boston (President); I. Chávez, Mexico City; D. E. Bedford, London; P. W. Duchosal, Geneva; F. D. Mayer, Chicago (attorney); Mrs. J. Stern (secretary). The Treasurer is L. N. Katz, Chicago.

Several research workers from various countries have already received sizable support from this Foundation. Applications should be sent to the President.

This commendable Foundation should be fully supported and constantly provided with means for its activities. As a particularly praiseworthy example of cooperation, we would like to single out the generous contribution of the Finnish Society of Cardiology.

We invite the financial support of all persons wishing to contribute to the progress in cardiovascular research at the international level, and we kindly request the readers of this Journal to give their constructive attention to our appeal and to make it known.

Am. Heart J.
June, 1959

THE 6TH INTERNATIONAL CONGRESS FOR INTERNAL MEDICINE will be held in Basel, Switzerland, from August 24 through 27, 1960. The Congress will be organized in conjunction with the Swiss Society for Internal Medicine.

For further details, write to the Secretariat of the 6th International Congress for Internal Medicine, 13, Steinentorstrasse, Basel, Switzerland.

THE FOURTH INTERNATIONAL CONGRESS OF THE INTERNATIONAL CARDIOVASCULAR SOCIETY will be held in Munich, Germany, Sept. 18-20, 1959. Address correspondence to Dr. Henry Haimovici, Secretary-General, 715 Park Avenue, New York 21, N. Y.

THE TENTH ANNUAL FISK UNIVERSITY INFRARED SPECTROSCOPY INSTITUTE will be held in Nashville, Tenn., at Fisk University, August 24-29, 1959.

The Fisk Infrared Institute is designed to provide chemists, physicists, engineers, and medical scientists with sufficient background training to make effective use of infrared spectroscopy in their laboratories.

Further information as well as application forms may be obtained by writing to Nelson Fuson, Director, Infrared Spectroscopy Institute, Fisk University, Nashville 8, Tenn.

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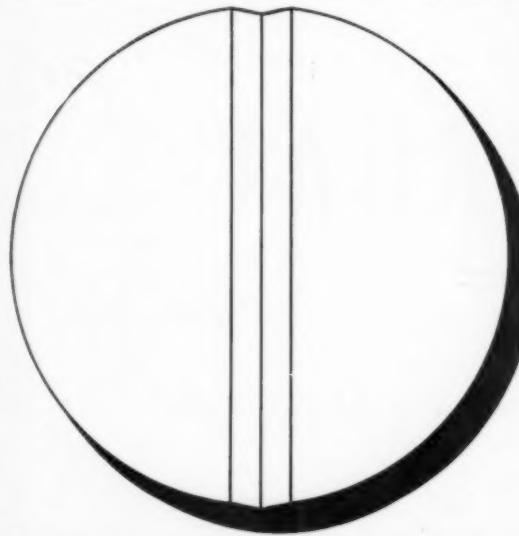
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Review of Books.—Publishers and authors are informed that the space of the Journal is so fully occupied by matter pertaining to the branches to which it is devoted that only works treating of these subjects can be noticed. Books and monographs on the anatomy, physiology, pharmacology, therapeutics, and pathology of the heart, blood vessels, and circulation, will be reviewed when space is available. Send books to the Editor, Dr. George E. Burch, 1430 Tulane Avenue, New Orleans 12, Louisiana.

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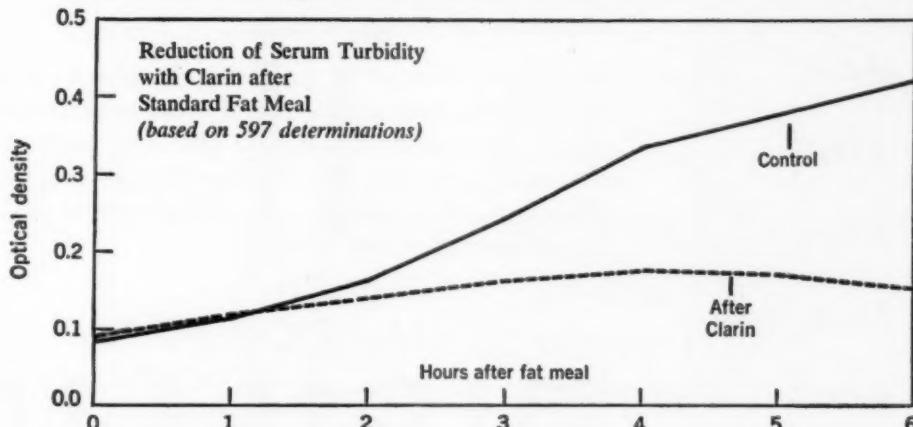
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1. Council on Drugs, J.A.M.A. 166:52 (Jan. 4) 1958.
2. Hahn, P. F.: Science 98:19 (July 2) 1943.
3. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
4. Rubio, F. A., Jr.: Personal communication.
5. Engelberg, H., et al.: Circulation 13:489 (April) 1956.

*Trade Mark. Patent applied for.

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1. Lade, R.I., et al.: Pediatrics 21:238 (Feb.) 1958.



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Weight: 210 pounds



B.P.: 170/112 mm. Hg
Nervous
Sweating palms

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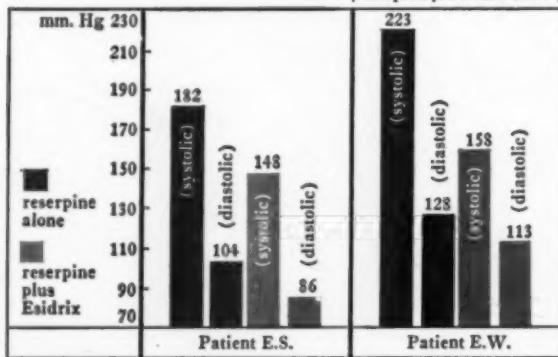
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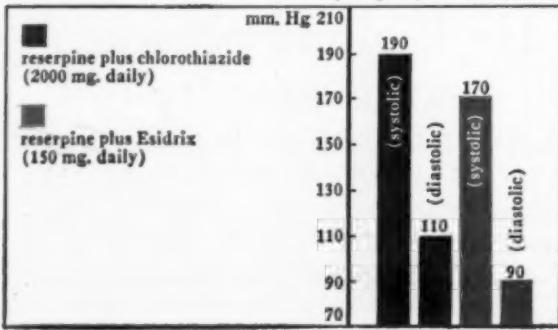
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References—1. Maronde, R. F.: Clinical Report to CIBA.
2. Greenstein, S.: Clinical Report to CIBA.

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References: 1. Russek, H. I.: Postgrad. Med. 19: 562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1956.

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(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

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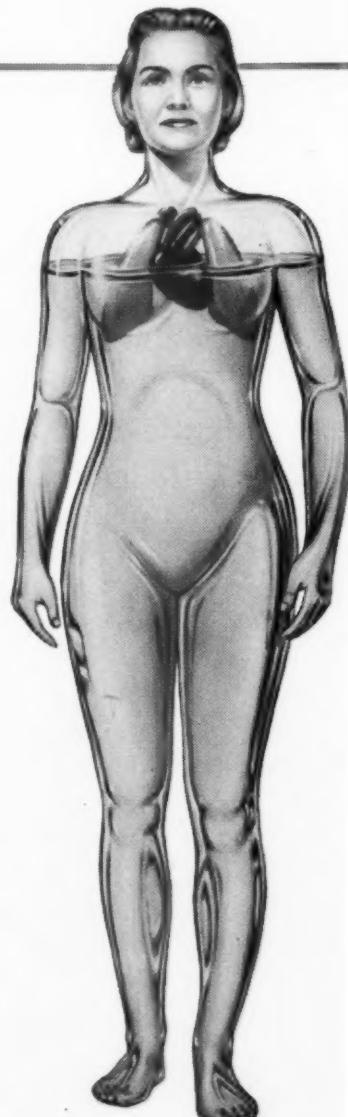
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bibliography: 1. Esch, A. F., Wilson, I. M. and Freis, E. D.: 3,4-Dihydrochlorothiazide: Clinical Evaluation of a New Saluretic Agent. Preliminary Report; M. Ann. District of Columbia 28:9, (Jan.) 1959. 2. Ford, R. V.: The Clinical Pharmacology of Hydrochlorothiazide; Southern Med. J. 52:40, (Jan.) 1959. 3. Fuchs, M., Bodl, T., Irie, S. and Moyer, J. H.: Preliminary Evaluation of Hydrochlorothiazide ("HYDRODIURIL"); M. Rec. & Ann. 51:872, (Dec.) 1958. 4. Moyer, J. H., Fuchs, M., Irie, S. and Bodl, T.: Some Observations on the Pharmacology of Hydrochlorothiazide; Am. J. Cardiol. 3:113, (Jan.) 1959.



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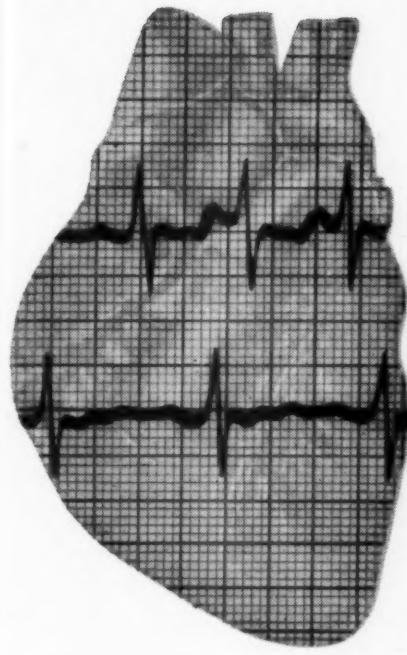
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*Feinblatt, T.M. and Ferguson, E.A.: New Eng. J. of Med. (Feb. 21) 1957.

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1. Smith, J. M.: Lederle Bull. Symposium Report, 1:1, 1958.
2. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

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*Amsterdam, B.: New York J. Med. 58:2199-2212 (July 1) 1958. Panel Discussion on Proper Nutrition for the Older Age Group, J. Am. Geriatrics Soc. 6:787-802 (Nov.) 1958. Leckert, J. T.; Donovan, C. B.; McHardy, G., and Cradic, H. E.: J. Louisiana M. Soc. 110:260-266 (Aug.) 1958.

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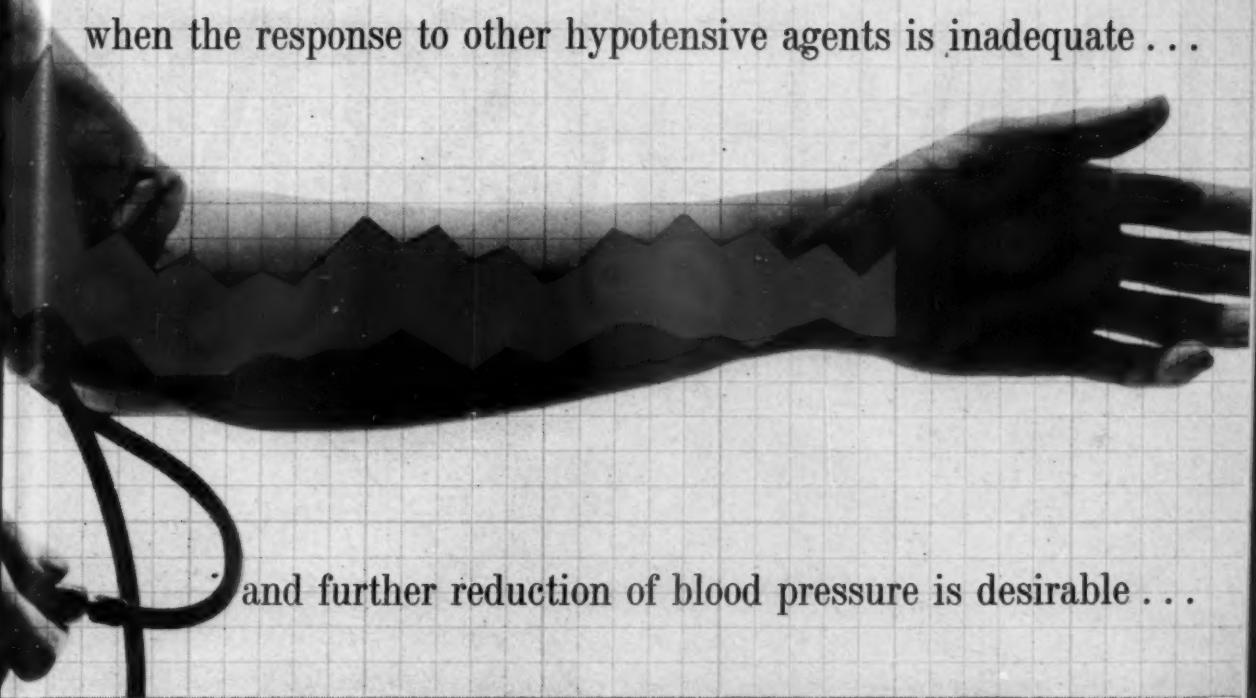


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"When employed under carefully controlled conditions with adequate attention to proper regulation of dosage, mecamylamine ['INVERSINE'] may be expected to reduce blood pressure effectively and to ameliorate various manifestations of hypertensive-cardiovascular disease. These include such symptoms as headache, dizziness, vertigo, hypertensive encephalopathy, cerebral or subarachnoid hemorrhage, retinopathy, cardiac hypertrophy and, in some cases, cardiac decompensation."

A.M.A. Council on Drugs, New and Nonofficial Drugs: Philadelphia, J. B. Lippincott Co., 1958, p. 285

**A GREATLY IMPROVED GANGLIONIC BLOCKING AGENT
'INVERSINE'**

- of the orally effective blocking agents, only 'INVERSINE' is completely and uniformly absorbed
- because it is uniformly absorbed, 'INVERSINE' provides predictable, reproducible effects with minimal day-to-day fluctuations
- has a gradual onset of effect, reducing the likelihood of sudden drops in blood pressure
- effective in extremely low dosage (orally, 10 mg. 'INVERSINE' is approximately equivalent to 100 mg. pentolinium, 80 mg. chlorisondamine, 1000 mg. hexamethonium)
- has a long duration of action (6 to 12 hours or longer), permitting convenient dosage schedules
- development of tolerance is not as pronounced as with other ganglionic blocking drugs
- effective in many patients who do not respond to other ganglionic blocking drugs

pretreatment with 'Diuril', or 'Diuril' and rauwolfia, enhances therapy with 'Inversine'

"Pretreatment with chlorothiazide ['DIURIL'] and rauwolfia reduces the dosage requirement, augments blood pressure response, and moderates certain of the side effects of ganglion blocking agents. Although such basal therapy is advantageous, unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension."

Beem, J. R., and Moyer, J. H.: Geriatrics 13:378, June 1958

dosage recommendations for new patients

1. Initiate therapy with 'DIURIL'

'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. Add other agents

Other drugs (rauwolfia, 'INVERSINE', hydralazine, etc.) are added as necessary and their dosage adjusted according to patient response.

'INVERSINE' is given in the same manner whether used with other drugs or alone. Recommended initial dosage is 2.5 mg. twice a day, pref-

erably after meals. May be increased by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'INVERSINE' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

3. Adjust dosage of all medication

The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

Precautions: Side effects of 'INVERSINE' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'INVERSINE' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction. Additional information on 'INVERSINE' and 'DIURIL' is available on request.

Supplied: 'INVERSINE', tablets of 2.5 and 10 mg. Bottles of 100.

'DIURIL', tablets of 250 mg. and 500 mg. Bottles of 100 and 1000.



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The "Maximum Security" Anticoagulant

FASTER, MORE PRECISE ADJUSTMENT OF PROTHROMBIN LEVEL

After recovery from a myocardial infarction, DANILONE — the "maximum security" anticoagulant — guards the patient against the inevitable¹ subsequent recurrence with less risk of hemorrhage. Unlike dicumarol and related coumarin derivatives, DANILONE has a short latent and a short recovery period, and therefore, noncumulative action. Thus, the prothrombin level may be rapidly and accurately adjusted upward or downward by simple alteration of oral dosage. DANILONE may even be administered to many patients with shock, debilitation, hepatic, renal or gastrointestinal disease even though coumarin derivatives might be dangerous. The practical advantages of DANILONE are well documented.

EARLY ONSET "...approximately twice as fast in reaching therapeutic levels as is dicumarol."²

FASTER DISSIPATION "...rapid return to a normal level in the event of undue prolongation of prothrombin time or hemorrhage."³ (After withdrawal of DANILONE, recovery is well advanced in 24 hours, complete in 40 hours — as opposed to 7 days for dicumarol).

GREATER SAFETY "...can be administered with reasonable safety in the presence of many conditions which would contraindicate the use of dicumarol."⁴

The short latent period and rapid recovery allow the physician to obtain even more satisfactory control by dividing the daily dose into two twelve-hour intervals.

"An advantage of a twelve-hour dosage schedule is that only half the daily dose may have been given when bleeding or excess prothrombin effect is discovered, allowing earlier adjustment of dosage or discontinuance."⁴

ECONOMICAL "...We have found phenindione inexpensive..."

PREDICTABLE "...and relatively easy to manage with a reasonably constant daily dosage."³

Samples and literature available on request.

Supplied: In 50 mg. scored tablets, bottles of 100 and 1,000.

1. Manchester, B.: Ann. Int. Med. 47:1202 (Dec.) 1957. 2. Harper, B. F. and Johnson, R.: J.M.A. Georgia 45:149 (April) 1956. 3. Wood, J. L. et al.: J.A.M.A. 159:635 (Oct.) 1955. 4. Sise, H. et al.: Am. Heart J. 53:132 (Jan.) 1957.

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*Harris, R., and Del Giacco, R. R.: Am. Heart J. 52:300, 1956.

†White's brand of amorphous gitalin.

‡Bibliography available on request.



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Arteriosclerotic Heart Disease



Consensus:
The preferred antidote
for anticoagulant-induced
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is 'Mephyton' (vitamin K₁).



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"...has a more prompt, more potent and more prolonged effect than the vitamin K analogues....Its reliability in treating undue hypoprothrombinemia from anticoagulant therapy is of particular importance. [Mephyton] can be depended on to reverse anticoagulant-induced hypoprothrombinemia to safe levels whether bleeding is only potential or actually has occurred."

Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1958, p. 620.

"For correction of the anticoagulant effect of the coumarin compounds, vitamin K₁ is much more effective than are the water-soluble preparations of menadione."

Barker, N. W.: Fundamentals of anticoagulant therapy, Minn. Med. 41:252, April 1958.

For coumarin overdosage, "Vitamin K₁, given intravenously, in an oil emulsion will act as soon as two hours after injection. It is the treatment of choice in such conditions."

Kupfer, H. G., and Kinne, D. R.: Anticoagulants, theoretical considerations and laboratory control, Virginia M. Monthly 85:230, May 1958.

"...I would strongly urge the use of vitamin K₁...if an antidote is necessary for the hypoprothrombinemia produced by the coumarin anticoagulants or the indandiones."

Meyer, O. O.: Use of anticoagulants in the treatment of coronary artery disease, Postgrad. Med. 24:110, Aug. 1958.

chemically identical with naturally-occurring vitamin K₁

Mephyton.[®]

Vitamin K₁

Dosage: Orally, to modify anticoagulant effects: 5 to 10 mg. initially; 15 to 25 mg. for more vigorous action. Intravenously, for anticoagulant-induced bleeding emergencies, 10 to 50 mg.; may be repeated as indicated by prothrombin time response. (Some clinicians advise their patients to keep a supply of tablets on hand at all times; if gross bleeding occurs, the patients are instructed to take 10 mg. and phone the doctor.)

Supplied: Tablets, 5 mg.; bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg.; boxes of 6 ampuls.

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- well tolerated

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- prolonged, stable effect evenly sustained with single, low, daily dose^{5,7}
- ready reversal of action^{5,8}
- well tolerated^{5,6,8}

(1) Mayer, G. A., and Connell, W. F.: Canad. M.A.J. 77:930 (Nov. 15) 1957.

(2) Burke, G. E., and Wright, I. S.: Circulation 3:164, 1951.

(3) Vander Veer, J. B.; Funk, E. H., Jr.; Boyar, F. R., and Keller, E. A.: Am. J. Med. 14:694, 1953.

(4) Scovrone, L. A.; Beck, D. F., and Wright, I. S.: Circulation 6:489, 1952.

(5) Neill, E. C.; Moon, R. Y., and Vander Veer, J. B.: Circulation 15:713, 1957.

(6) Ruffo, F. R.; Bartels, C. C., and Evans, J. A.: J.A.M.A. 168:743 (Oct. 11) 1958.

(7) Menendez, C.; Almonte, J. C., and Ramos, C. N.: Angiology 8:182, 1957.

(8) Mayer, G. A., and Connell, W. F.: Canad. M.A.J. 76:272 (Feb. 15) 1957.

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well tolerated systemically and locally . . .

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" . . . excellent opacification was obtained in a high percentage of the patients . . ." Dennis, J.M.: Clinical Report to the Squibb Institute for Medical Research, March, 1956.

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Babaianz, L., and Wieser, C.: Praxis 44:454 (May 19) 1955.

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RATIONALE

"It appears that there is now available in chlorothiazide a drug which is a specific antagonist to the abnormal sodium metabolism seen in the vast majority of hypertensive patients. The use of this agent [DIURIL] may stand the test of time as the most vital and specific weapon in the treatment of a relatively non-specific disease in which the only specific abnormality known is one of sodium metabolism. . . .

Chlorothiazide now appears to be the drug of choice when initiating therapy in the average hypertensive patient."

Reinhardt, D. J.:
Delaware State Med. J. 30:1, January 1958.

RESULTS

"We have presented a group of 48 patients previously treated with a variety of antihypertensive agents." "Upon the addition of chlorothiazide to their regimens, there was realized an additional blood pressure lowering effect of 23 mm. systolic and 11 mm. diastolic."

Bunn, W. H., Jr.:
Ohio State Med. J. 54:1168, September 1958.

MINIMAL SIDE EFFECTS

"There is an extremely wide range between therapeutic and toxic dosage, and no significant side effects and no sensitivity to the drug as yet have been observed." ". . . it seems desirable to add potassium chloride 4 Gm. per day . . . in cases of hypertension. . . ."

Herrmann, G. R., Heitmancik, M. R., Graham, R. N. and Marburger, R. C.:
Texas State J. of Med. 54:639, September 1958.

dosage: one 250 mg. tablet DIURIL b.i.d. to one 500 mg. tablet DIURIL t.i.d.

supplied: 250 mg. and 500 mg. scored tablets DIURIL (Chlorothiazide) bottles of 100 and 1000.

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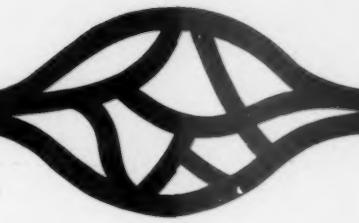
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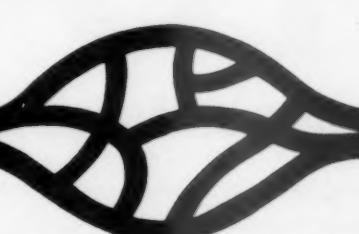
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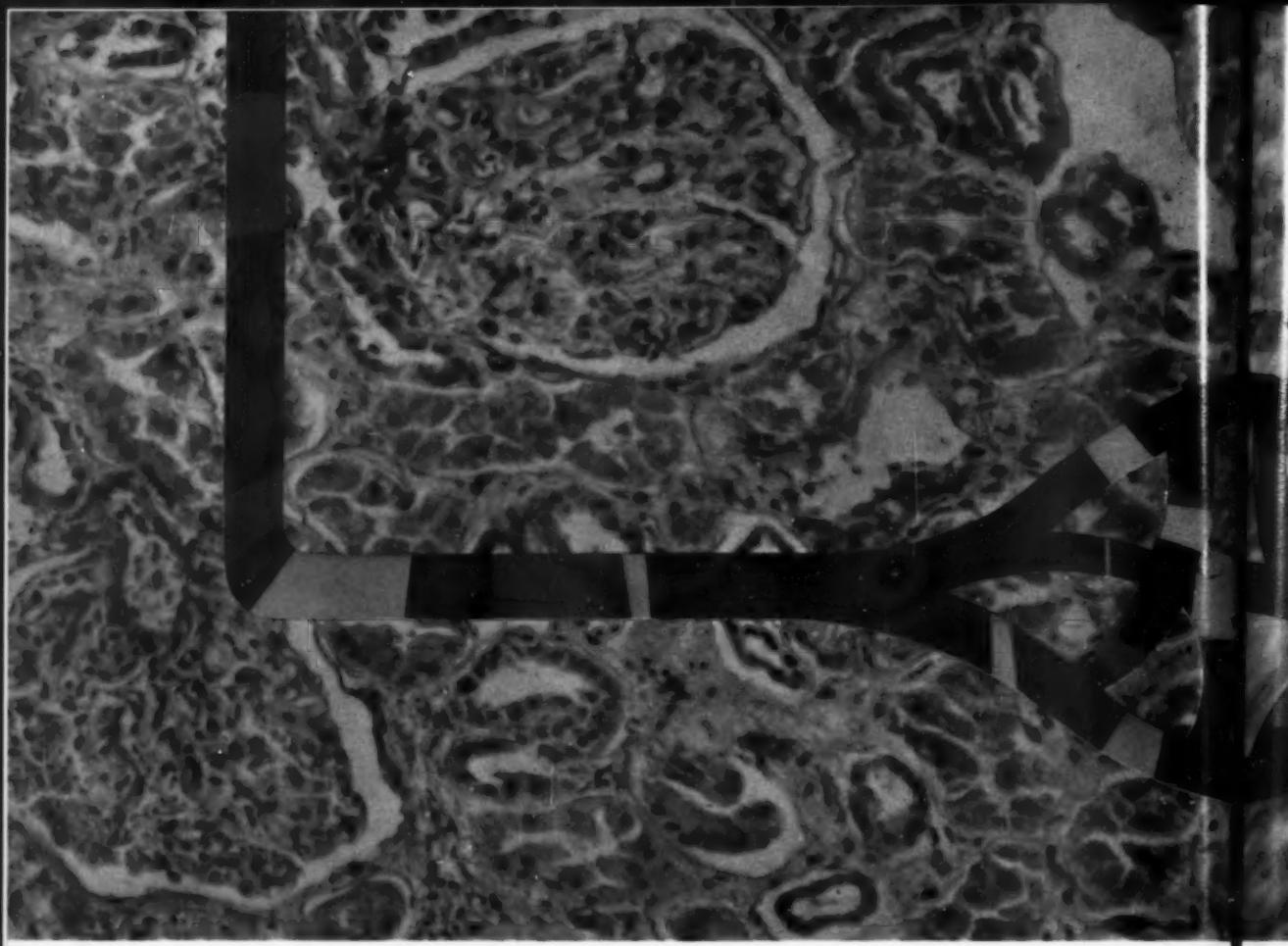
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Rautrax combines Raudixin with flumethiazide for control of all degrees of hypertension. Clinicians report it safely and rapidly eliminates excess extracellular sodium and water without potassium depletion.^{1,2,3} Through this dependable diuretic action of flumethiazide, the clinical and subclinical edema—so often associated with cardiovascular disease—is rapidly brought under control.^{2,3,4,5} Flumethiazide also potentiates the antihypertensive action of Raudixin. By this unique dual action, a lower

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Dosage: 2 to 6 tablets daily in divided doses initially; may be adjusted within range of 1 to 6 tablets daily in divided doses. **Note:** In hypertensive patients already on ganglionic blocking agents, veratrum and/or hydralazine, the addition of Rautrax necessitates an immediate dosage reduction of these agents by at least 50%. A similar reduction is also necessary when these ganglionic blocking agents are added to the Rautrax regimen.

Supply: Capsule-shaped tablets each providing 50 mg. Raudixin, 400 mg. flumethiazide, and 400 mg. potassium chloride, bottles of 100.

References: 1. Moyer, J.H., and others: Am. J. Cardiol., 3:113 (Jan.) 1959. • 2. Bodi, T., and others: To be published, Am. J. Cardiol., (April) 1959. • 3. Fuchs, M., and others: Monographs on Therapy, 4:43 (April) 1959. • 4. Montero, A.C.; Rochelle, J.B., III, and Ford, R.V.: To be published. • 5. Rochelle, J.B., III; Montero, A.C., and Ford, R.V.: To be published. • 6. Montero, A.C.; Rochelle, J.B., III, and Ford, R.V.: To be published. • 7. Doffermyer, L.R.; Byrd, C.W., and Lilly, W.H.: North Carolina M.J. 19:430 (Oct.) 1958.

Literature available on request.

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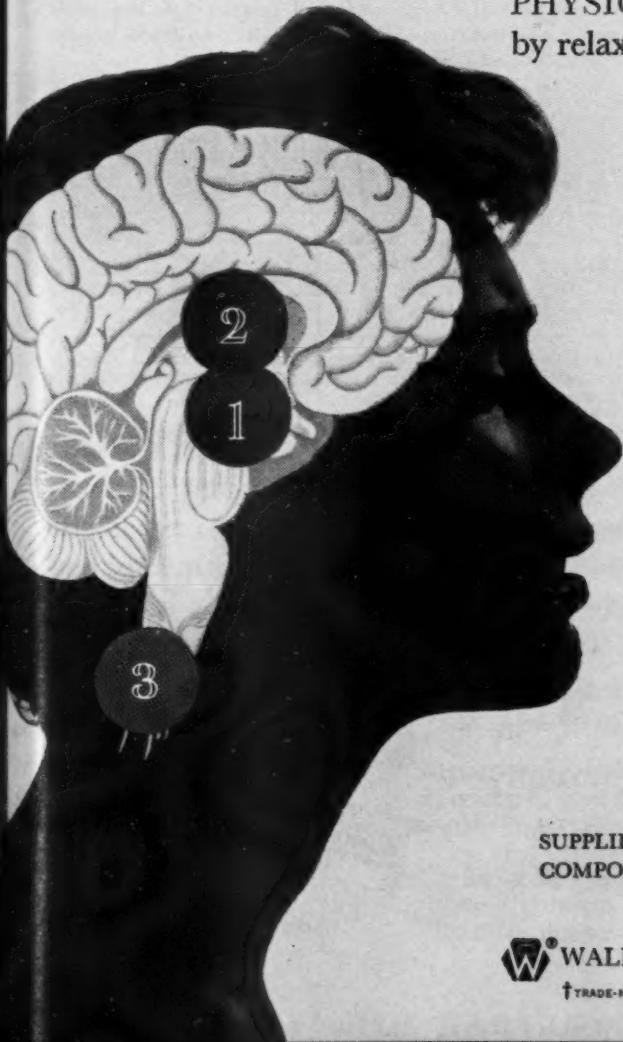
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	Tryptophan	Phenylalanine	Lysine	Threonine	Valine	Methionine	Leucine	Isoleucine
Essential Amino Acids Pattern in Quaker Oats Breakfast Dish* (1)	1.0	3.8	4.2	2.9	4.7	1.4	6.4	4.3
Essential Amino Acids Pattern Required by Male Adults (2)	1.0	4.4	3.2	2.0	3.2	4.4	4.4	2.8

*Prepared from 1 oz. Quaker Oatmeal (dry) and 4 fl. oz. whole milk.

(1) Estimated from values in "Amino Acid Content of Foods", Home Economics Research Report No. 4, U.S. Dept. Agr., 1957, pp. 48, 58.
(Quaker Oats protein = 16.7%)

(2) Staff Report: "Rose Reports Human Amino Acid Requirements", Chem. Eng. News 27:1364 (1949).

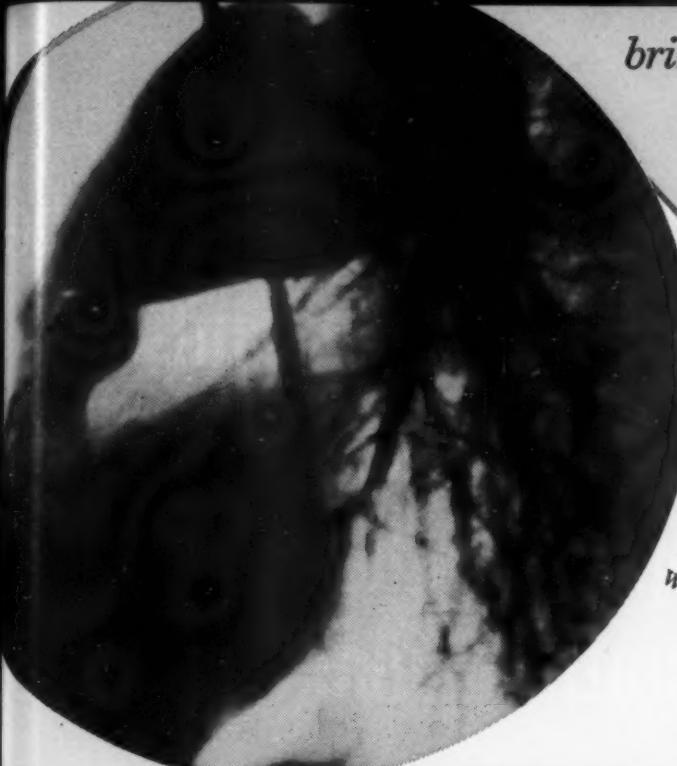
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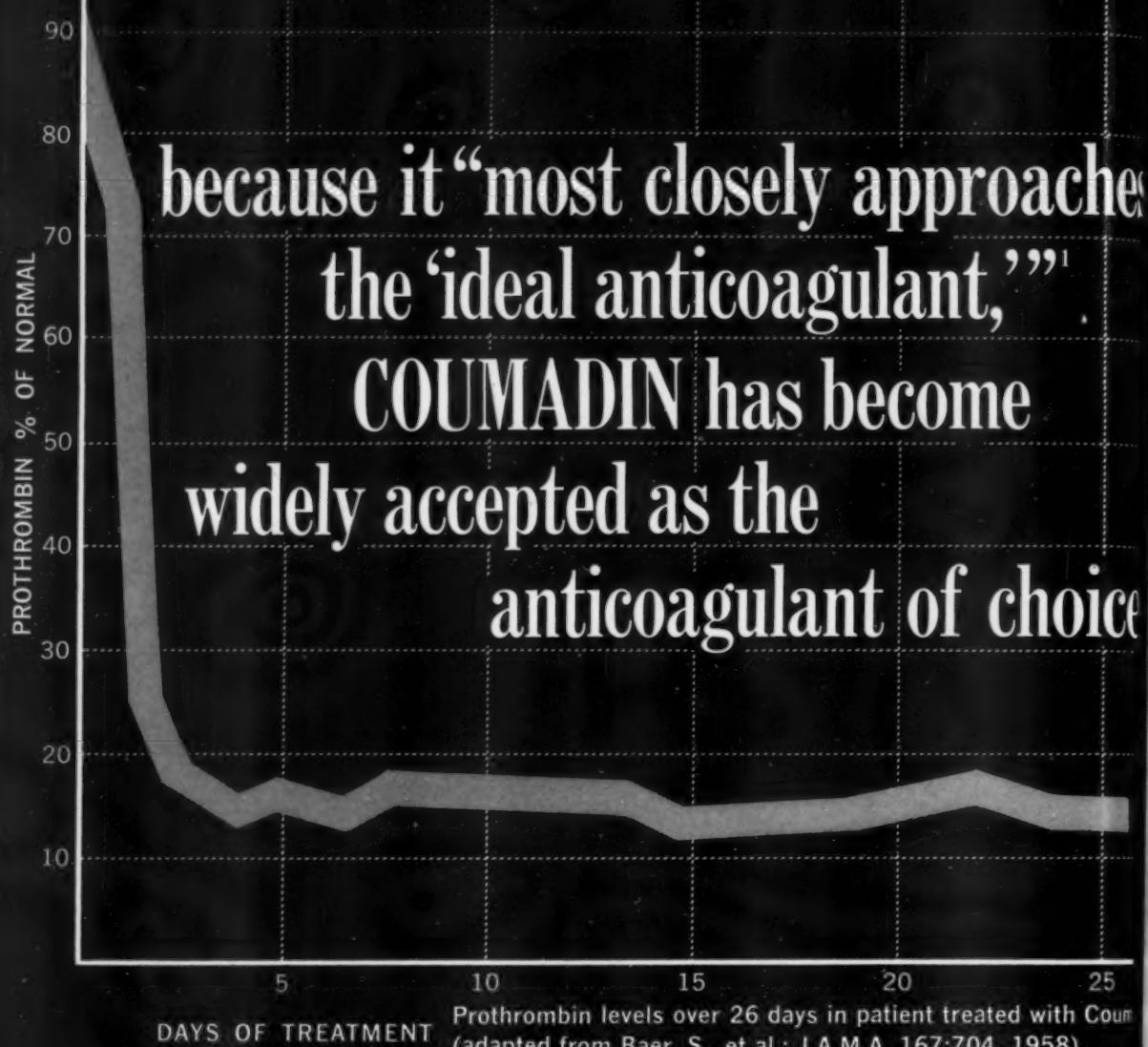
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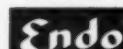
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COUMADIN (warfarin) Sodium—manufactured under license from the Wisconsin Alumni Research Foundation—developed for clinical use by Endo.

References: 1. Baer, S., et al.: J.A.M.A. 167:704, 1958. 2. Link, K. P.: Circulation 19:97, 1958. 3. Meyer, O. O.: Postgrad. Med. 24:110, 1958.

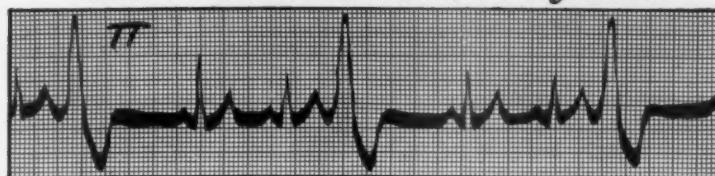
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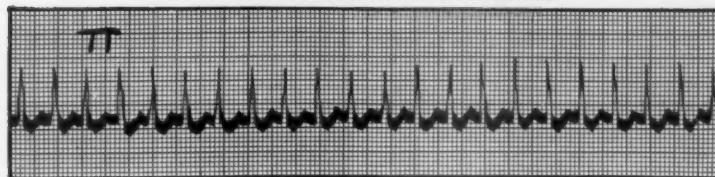
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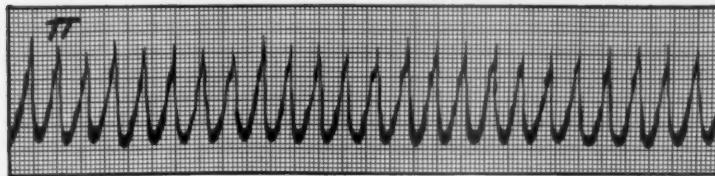
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Vistaril is effective in ventricular extrasystoles and paroxysmal tachycardias (both auricular and ventricular).

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proven calming action indicated for arrhythmia patients.

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of Vistaril as compared to other antiarrhythmic drugs in general use has been noted by investigators.

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(individualized by the physician for maximum effectiveness):

PARENTERAL DOSAGE: 50-100 mg. (2-4 cc.) I.M. stat., and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d. In acute emergency, 50-75 mg. (2-3 cc.) I.V. stat.; maintain with 25-50 mg. (1-2 cc.) I.V. q. 4-6 h., p.r.n.

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References: 1. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 2. Hucheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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Record of patient with congestive failure, treated at a leading Philadelphia hospital. Photos used with permission of the patient.

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(reserpine CIBA)

for the anxious hypertensive with or without tachycardia



L.S., 81-year-old patient with complaint of painless hematuria admitted to hospital on 3/3/59. Past history included congestive heart failure of 15 years' duration. **Clinically significant symptoms:** expiratory wheezes over entire chest; bilateral coarse rales of both bases; slight abdominal distention (without evidence of ascites); palpable liver 2-3 fingerbreadths below rib cage; bilateral pitting edema (4+) of pretibial and ankle areas. **Admission diagnosis:** hematuria of unknown origin; arteriosclerotic cardiovascular disease; poorly compensated heart failure; chronic pulmonary fibrosis with pulmonary insufficiency.

Patient was put on regimen of bed rest, moderate salt restriction, digitalis and pulmonary decongestants. When ankle edema, hepatic congestion and rales failed to clear by 3/6, Esidrix 50 mg. b.i.d. was ordered. By 3/8 L.S. had lost 3 pounds. Rales decreased; there was 1+ pitting edema of ankle area only. He felt more comfortable, was able to enjoy reading newspapers and magazines in bed.

Ambulatory on the 4th day of Esidrix therapy, L.S. visited his neighbors down the hall, played checkers with another patient. There was no evidence of ankle edema. By 3/11, patient's weight had dropped 2 more pounds and rales were gone. Patient tolerated cystoscopy and fulguration of a small bleeding polyp in his bladder on 3/12 very well. On 3/14 he was discharged.

Patient L.S.	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13
Urinary Output (ml.)	840	690	960	2140	1230	660	1220	1350	--	--
Weight (lbs.)	139	--	--	--	136	--	--	134	--	--
Esidrix Dosage (mg./day)	0	0	50	100	100	100	100	100	50	100

Esidrix^{T.M.}

(hydrochlorothiazide CIBA)

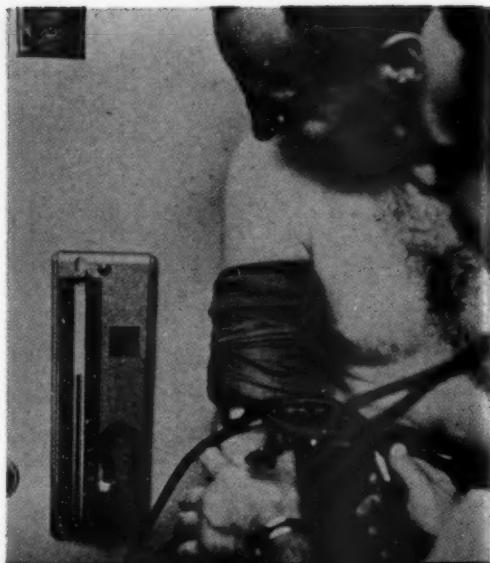
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1. Brest, A. N., and Likoff, W.: Am. J. Cardiol. 3:144 (Feb.) 1959. 2. Clark, G. M.: Clinical report to CIBA.
3. Dennis, E. W.: Clinical report to CIBA.

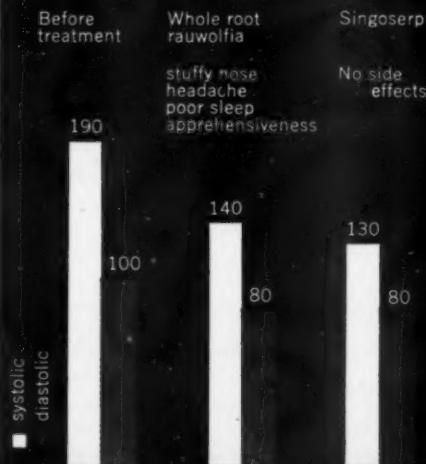
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PHOTOS USED WITH PERMISSION OF THE PATIENT.

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- more than half of these patients suffered from moderate to severe hypertension
- more than half of the cases involved hypertension of at least 6 years' standing, with many histories of up to 20 years' duration

THE SIDE-EFFECTS PROBLEM WAS MINIMIZED IN MOST PATIENTS:

Chart shows gratifyingly low incidence of side effects in 233 patients given Singoserp with no other antihypertensive medication



Side Effect	Number	Per Cent
Lethargy	7	2.9
Headache	6	2.5
Gastrointestinal upset	3	1.2
Vertigo	2	0.8
Nasal congestion	1	0.4

DOSAGE:

In new patients: Average initial dose, 1 to 2 tablets (1 to 2 mg.) daily. Some patients may require and will tolerate 3 or more tablets daily. Maintenance dose will range from ½ to 3 tablets (0.5 to 3 mg.) daily.

In patients taking other antihypertensive medication: Add 1 to 2 Singoserp tablets (1 to 2 mg.) daily. Dosage of other agents should be revised downward to a level affording maximal control of blood pressure and minimal side effects.

a major improvement in rauwolfia

a major advance in antihypertensive therapy

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SUMMIT, N.J.

2/55589K

June, 1959

Page 45

after a coronary

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provide prolonged vasodilatation

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Mercury-Sparing

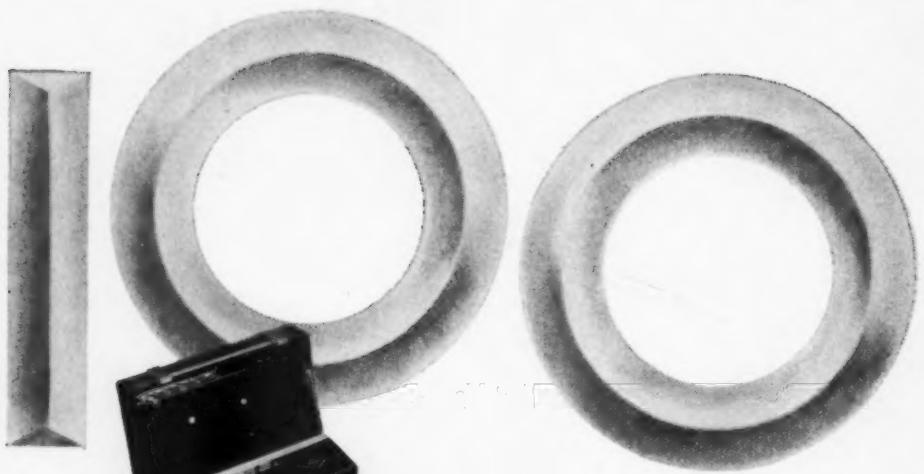
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1. Asher, G.: Personal communication, June 23, 1956.
2. Settel, E.: Rolicton® (Aminoisometradine), a New, Non-mercurial Diuretic, Postgrad. Med. 21:186 (Feb.) 1957.
3. Goldner, M. G.: Personal communication, June 29, 1956.

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Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: Am. J. M. Sc. 234:150, Aug. 1957.

2. Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Am. J. M. Sc. 233:280, March 1957. 3. Boyd, L. J., Huppert, V. F., Mullinos, M. G. and Hammer, H.: Am. J. Cardiol. 3:229, Feb. 1959.

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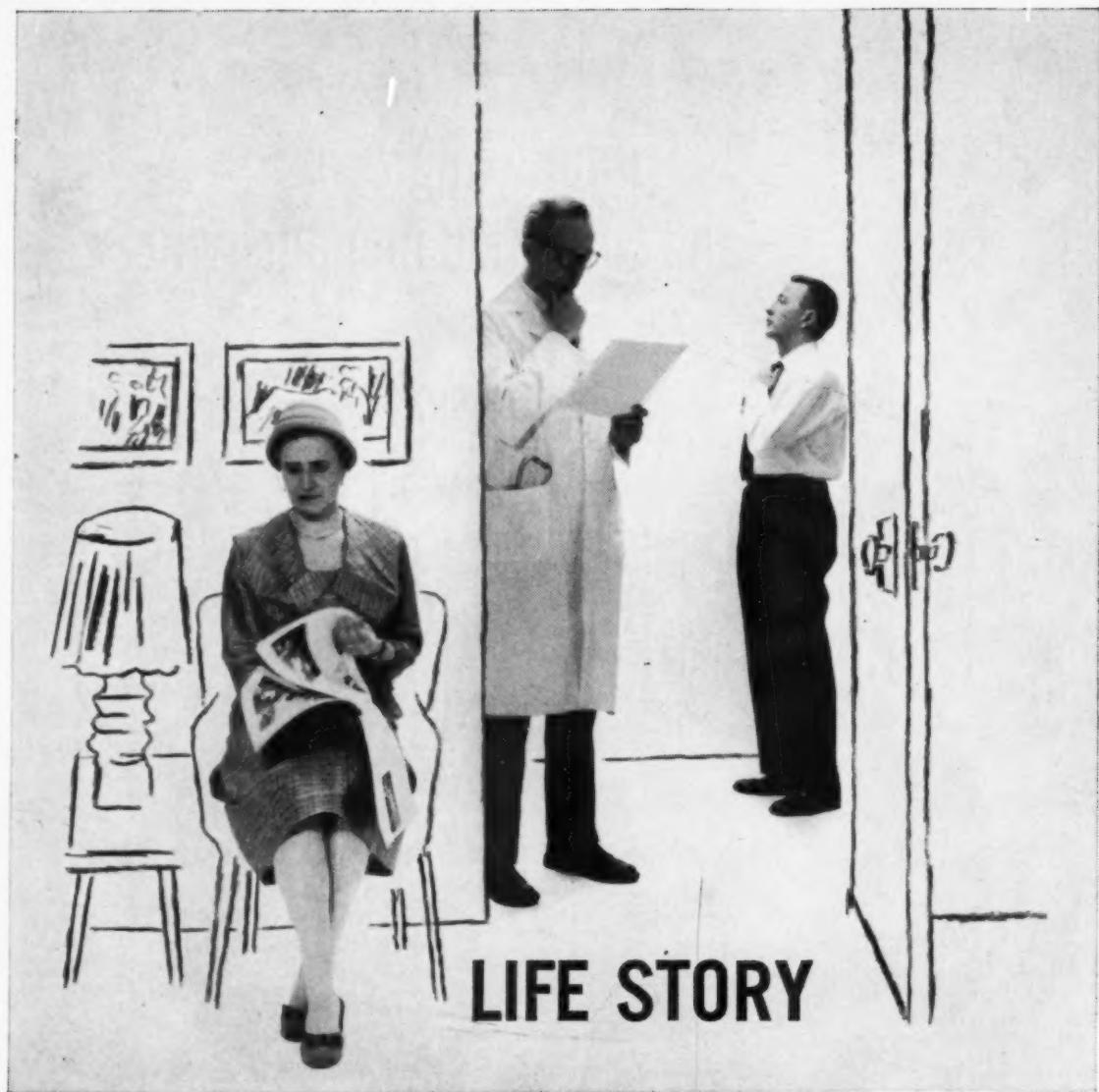
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References: 1. Russek, H. I.: Postgrad. Med. 19: 562 (June) 1966. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1968.

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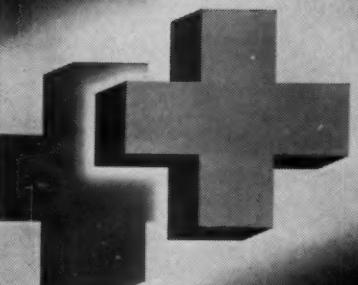
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1. Seizer, A. and Ryland, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.



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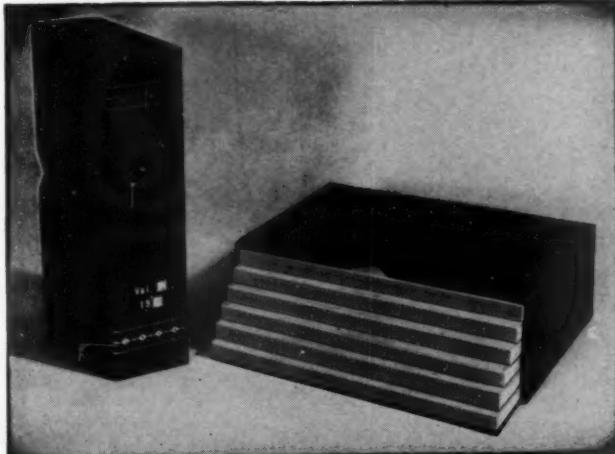
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